



Oxford Textbook of Old Age Psychiatry (3 edn)

Edited by Tom Denning, Alan Thomas, Robert Stewart, and John-Paul Taylor

[Previous Edition \(2 ed.\)](#)

Abstract

The Oxford Textbook of Old Age Psychiatry, Third Edition, has been thoroughly updated to keep pace with the developments that have taken place in old age psychiatry since publication of the Second Edition in 2013, including the publication of the DSM-5/ICD-11 classification criteria. The Third Edition also includes new chapters on the ageing brain; the experience of dementia; carers' issues; biomarkers; and old age psychiatry in low- and middle-income countries. This is an essential reference for old age psychiatrists, geriatricians, and other clinicians who are interested in the mental health care of older people.

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Dedication



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Dedication 📖

Author(s): Tom Denning

To our families, with love and gratitude

TD, AT, RS, JPT



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Preface

Author(s): Tom Denning

Welcome to the third edition of the *Oxford Textbook of Old Age Psychiatry* !

Although it is the third edition of this title, the book has a longer ancestry. In 1965, the late Felix Post published *Clinical Psychiatry of Late Life*, undoubtedly one of the earliest texts in our field. The gap left when this book went out of print was filled by Robin Jacoby and Catherine Oppenheimer's *Psychiatry in the Elderly*, which appeared in 1991. This book was revolutionary in its inclusion of highly practical chapters dedicated to topics such as driving and mental capacity that were not available elsewhere. The fourth edition of *Psychiatry in the Elderly* became the first edition of this Oxford Textbook.

Over the period covered by these successive publications, the numbers of older people have grown worldwide and continue to do so. Changing birth rates, work patterns, trends in migration, and diverse economic forces are transforming our societies. At the same time, we are all learning to live in an increasingly electronic and digitalized world. All of these factors impact upon older people; on the mental disorders that they may

Preface

experience; and upon the way in which treatment, support, and care can be organized. Meanwhile, dementia has been rightly recognized as one of the most salient global public health issues. Increasingly, individual countries are producing their own national dementia strategies. These vary in detail and as to whether any resources are actually committed; the simple fact that strategies exist is an important step forward. Dementia research has gained increasing attention, although there are concerns that disease-modifying drugs have been slow to emerge, as well as criticism that not enough research benefits people who have dementia now as opposed to those who may or may not develop it in future. Furthermore, it is important that all the attention on dementia does not divert our focus from other pressing mental health issues like depression and anxiety that are also highly prevalent and can be equally disabling. Nonetheless, we continue to live in exciting times, and this is something we should celebrate.

Inexorably, the amount and complexity of the content of this book has increased with each edition; so, too, has the number of authors. Thus, we have moved in just over 50 years from a single-author volume to needing something akin to an American football squad or a national Olympics team. For this edition we have reverted to four editors and we are delighted to welcome Rob Stewart and John-Paul Taylor to the editorial team.

The 'Jacoby and Oppenheimer' structure has proved extremely durable and we have retained this approach. The sections of the book start with basic sciences (both neurobiological and social science), followed by clinical practice, specific disorders, and service provision, before finishing again with ethical and legal issues.

Since the previous edition, we have introduced new chapters on biomarkers, carers, and issues in low- and middle-income countries. These not only reflect suggestions made after the last edition, but also our desire to cover topics that are of growing importance. We have also increased the number of contributions from people with lived experience, as we believe that these contributions are among the most-read chapters in the book. For any reader, whether they are a lay reader, student, trainee specialist, or established professional, these accounts provide material that brings the science alive.

Our team of authors has been refreshed. We pride ourselves that everyone we invite to contribute has agreed to do so, which reflects both the impact that this book has had and its excellent reputation. We also have maintained our international focus, since the book has a worldwide readership.

Of course, without the help of all our contributors, this book would not be possible, so we gratefully acknowledge your expertise, time, and commitment. Thank you all. And many thanks to our editors at Oxford University Press, Pete Stevenson, Lauren Tiley, and Rachel Goldsworthy,

Preface

who have been a pleasure to work with. Finally, thanks to older people—our patients, their families, our families, too—who have educated us all and helped us in this venture.

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Abbreviations

Author(s): Tom Denning

Symbols

α
alpha
 β
beta
 ε
epsilon
 γ
gamma
 κ
kappa
 μ
mu
\$
US dollar
 λ
lambda
™

Abbreviations

trademark

©

copyright

≥

±

(R)-PK11195

1-[2-chlorophenyl]-N-methyl-N-[1-methyl-propyl]-3-isoquinoline

carboxamide

¹²³I-IMP

N-isopropyl-(¹²³I)-p-iodoamphetamine

¹⁸F-FDG

¹⁸Fluorodeoxyglucose

¹¹C-PIB

¹¹C-Pittsburgh compound B

3C

The Three-City Study

3D

three-dimensional

3R

3-repeat

3R-tau

Three repeat sequences in the tau isoform

4R

4-repeat

4R-tau

Four repeat sequences in the tau isoform

5-I-A-85380

[(¹²³I)-5-iodo-3-[2(S)-azetidinylmethoxy]pyridine)

^{99m}Tc-ECD

^{99m}Tc-ethylcysteinate dimer

^{99m}Tc-HMPAO

^{99m}Tc-hexamethylpropyleneamine oxime

A

amyloid-beta

AA

Alcoholics Anonymous

AA

Alzheimer's Association

AASM

American Academy of Sleep Medicine

ABA

applied behavioural analysis

ABDQ

Adaptive Behaviour Dementia Questionnaire

ACC

anterior cingulate cortex

ACE III

Addenbrooke's Cognitive Examination III

Abbreviations

Ach
acetylcholine
AChE
Acetylcholinesterase
AChEIs
AChE inhibitors
ACP
advance care planning or advanced care plan
AD
Alzheimer's disease/Alzheimer's-type dementia
ADs
advance directives
ADAM10
a disintegrin and metalloprotease 10
ADAS-Cog
Alzheimer's Disease Assessment Scale—cognitive subscale
ADHD
attention deficit hyperactivity disorder
ADI
Alzheimer's Disease International
ADL
activities of daily living
a-DMR
age-differentially methylated region
ADNI
Alzheimer's Disease Neuroimaging Initiative
ADRT
advance decision to refuse treatment
ADS
Association for Dementia Studies
AEC
anticholinergic effect on cognition
aFTLD-U
atypical FTLD with ubiquitinated inclusions
AGD
argyrophilic grain disease
AGECAT
Automated Geriatric Examination Computer Assisted Taxonomy
AGES
Age, Gene/Environment Susceptibility (Study)
AHI
apnoea-hypopnoea index
AICD
APP interacellular cytoplasmic domain
AIDS
acquired immune deficiency virus
AISA
Adults with Incapacity (Scotland) Act 2000
AKAP9

Abbreviations

a kinase anchor protein 9
ALP
autophagy-lysosomal pathway
ALS
amyotrophic lateral sclerosis
aMCI/A-MCI
amnesic mild cognitive impairment
AMHP
approved mental health professional
APMI
Alzheimer Precision Medicine Initiative
APMI-CP
Alzheimer Precision Medicine Initiative cohort programme
APOE/ApoE
apolipoprotein E
APP
amyloid precursor protein
ARD
alcohol-related dementia
ARTAG
ageing-related tau astrogliopathy
ASL
arterial spin labelling
ASOs
anti-sense oligonucleotides
AST
aspartate aminotransferase
ASV
adaptive sero-ventilation
ATP
assistive technology
ATP
adenosine triphosphate
AUC
area under the curve
AUDADIS-IV
Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV
AUDs
alcohol use disorders
AVOW
Abuse and Violence against Older Women
B0
(external static) magnetic field
BACE1
beta-site amyloid precursor protein-cleaving enzyme 1
BBB
blood-brain barrier
BBBIG

Abbreviations

Blood-Based Biomarker Interest Group
BBB-PIA
Professional Interest Area focused on Blood-Based Biomarkers
BDNF
brain derived neurotrophic factor
BIBD
basophilic inclusion body disease
BME
black and minority ethnic
BMI
body mass index
BOLD
blood oxygen level dependent
BPSD
behavioural and psychological symptoms of dementia
BSE
bovine spongiform encephalopathy
BT
behaviour therapy
BtC
behaviours that challenge
bv-FTD
behavioural variant frontotemporal dementia
C9orf72
Chromosome 9 open reading frame 72
CAA
cerebral amyloid angiopathy
CAA
cerebral amyloid angiopathy
CADASIL
cerebral autosomal dominant arteriopathy with subcortical infarcts
and leukoencephalopathy
CAG
cytosine-adenine-guanine
CAIDE
Cardiovascular Risk Factors, Aging and Dementia
CAM
Confusion Assessment Method
CAMCOG
Cambridge Cognitive Exam
CAMDEX
Cambridge Mental Disorders of the Older Population Examination
cAMP
cyclic adenosine monophosphate
capCAA
capillary cerebral amyloid angiopathy
CARASIL
cerebral autosomal recessive arteriopathy with subcortical infarcts
and leukoencephalopathy

Abbreviations

CARE	Comprehensive Assessment and Referral Evaluation
CASPR2	contactin-associated protein 2
CATIE-AD	Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer’s Disease
CBD	corticobasal degeneration
CBS	corticobasal syndrome
CBSST	Cognitive-behavioural social skills training
CBT	cognitive behavioural therapy
CBTi	cognitive behaviour therapy for insomnia
CC75C	Cambridge City over-75s Cohort Study
CCF	comprehensive conceptualization framework
CCQI	College Centre for Quality Improvement
CDR	clinical dementia rating scale
C-ECT	continuation therapy
CERAD	Consortium to Establish a Registry for Alzheimer’s Disease
CES-D	Center for Epidemiologic Studies Depression
CFAS	Cognitive Function and Ageing Studies
CGA	Comprehensive Geriatric Assessment
CGA	comprehensive geriatric assessment
CGI-BP	Clinical Global Impression-Bipolar
CHAP	Chicago Health and Aging Project
CHCHD10	Coiled-coil-helix-coiled-coil-helix domain containing 10
CHD	coronary heart disease
ChEI	cholinesterase inhibitor
CHMP2B	Chromatin-modifying protein 2B

Abbreviations

Cho
choline
CIDI
Composite International Diagnostic Interview
CIND
Cognitive Impairment No Dementia
CIRA-Ar
Clinical Institute Withdrawal Assessment for Alcohol—Revised
CIRS-G
Cumulative Illness Rating Scale-Geriatrics
CJD
Creutzfeldt-Jakob disease
CLU
clusterin
CMFgl
cerebral metabolic rate for glucose
CMHT
community mental health team
CMHT
community mental health team
CNS
central nervous system
COPD
chronic obstructive pulmonary disease
COX
cytochrome c oxidase
CPA
Care Programme Approach
CPAP
continuous positive airways pressure
CPEAB
Caregiver Psychological Elder Abuse Behavior Scale
CPN
community psychiatric nurse
CPRS
Comprehensive Psychopathological Rating Scale
CQC
Care Quality Commission
Cre
creatine
CREB
cAMP response element-binding protein
CRP
C-reactive protein
CRPD
Convention on the Rights of Persons with Disabilities
CS
conditioned stimulus
CSA

Abbreviations

central sleep apnoea
CSD
cognitive spectrum disorder
CSF
cerebrospinal fluid
CSHA
Canadian Study of Health and Aging
CSQ
Caregiver Scenario Questionnaire
CSSRS
councils with social services responsibilities
CST
cognitive stimulation therapy
CT
computed tomography
CT1, CT2, CT3
Core Training Years 1-3
CTF
carboxyl terminal fragment
CTO
community treatment orders
CVR
conventional vocational rehabilitation
CXY
chest X-ray
DALY
disability-adjusted life years
DART-AD
Dementia Antipsychotic Withdrawal Trial
DAT
dopamine transporter
DaTscan
dopamine transporter scan
DBP
diastolic blood pressure
DBS
deep brain stimulation
DCBMAS
Dementia Care Behaviour Management Advisory Service
DCTN1
Dynactin-1
DD
delusional disorder
DH
Department of Health
DIADS-2
Depression in Alzheimer's Disease Study Phase II
DiSDAT
Disability Distress Assessment Tool

Abbreviations

DLB	dementia with Lewy bodies
DLD	Dementia Questionnaire for People with Learning Disabilities
DLDH	dementia lacking distinctive histopathology
DLPFC	dorsolateral prefrontal cortex
DMN	default mode network
DN	dystrophic neurite
DNA	deoxyribonucleic acid
DNAmAg	DNA methylation age
DoL	deprivation of liberty
DoLs	Deprivation of Liberty Safeguards
DOS	Delirium Observation Screening
DPA714	N,N-diethyl-2-[4-(2-fluoroethoxy)phenyl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-acetamide
DPPX	dipeptidyl-peptidase-like protein
DPRs	Dipeptide repeat proteins
DPSD	Dangerous People with Severe Personality Disorder
DPUK	Dementias Platform UK
DR	dietary restriction
DSC-MRI	dynamic susceptibility MRI
DSCU	Dementia Special Care Unit
DS-DAT	Discomfort Scale—Dementia of Alzheimer Type
DSI	Depression Status Inventory
DSQIID	Dementia Screening Questionnaire for Individuals with Intellectual Disabilities
DSQIID	Dementia Screening Questionnaire for Individuals with Intellectual Disabilities

Abbreviations

DSST	Digit Symbol Substitution Test
DTI	diffusion tensor imaging
DVLA	Driver and Vehicle Licensing Agency
DWI	diffusion-weighted imaging
EAI	Elder Assessment Instrument
EAPC	European Association of Palliative Care
EASI	Elder Abuse Suspicion Index
ECA	Epidemiologic Catchment Area
ECD	Ethylcysteinate dimer
ECG	electrocardiogram
ECHR	European Convention of Human Rights
EClipSE	Epidemiological Clinicopathological Studies in Europe
ECT	electroconvulsive therapy
EDR	elderly dependency ratio
EDS	excessive daytime sleepiness
EDS	excessive daytime sleepiness
EEG	electroencephalography
eGFR	estimated glomerular filtration rate
ELIMSA	enzyme-linked immuno-mass spectrometric assay
ELISA	enzyme-linked immunosorbent assay
ELSA	English Longitudinal Study of Ageing
EMBLEM	European Mania in Bipolar Longitudinal Evaluation of Medication
EMG	electromyogram
EMI	elderly mentally ill
ENS	

Abbreviations

enteric nervous system
EOAD
early-onset Alzheimer's disease
EOD
early-onset depression
EOG
electro-oculogram
EOS
early-onset schizophrenia
EPA
Enduring Powers of Attorney
EPAD
European Prevention of Alzheimer's Consortium
EPAP
expiratory positive airway pressure
EPAS
Elders' Psychological Abuse Scale
EPESE
Established Populations for Epidemiologic Studies of the Elderly
EPS
extrapyramidal symptoms
ERD
event-related desynchronization
ERF
event-related field
ERP
event-related potential
ERS
event-related synchronization
ESR
erythrocyte sedimentation rate
ESS
Epworth Sleepiness Scale
EWAS
epigenome-wide association studies
FA
fractional anisotropy
FAF
Familial amyloidosis of Finnish type
FAST
Functional Adaptation Skills Training
FBC
full blood count
FBD
familial British dementia
FCSRT
Free and Cued Selective Reminding Test
FD
Fabry disease

Abbreviations

FDA
Food and Drug Administration
FDD
familial Danish dementia
FDDNP
2-(1-{6-[(2-[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl}-
ethylidene)malononitrile
FDG
Fluorodeoxyglucose
FDG-PET
¹⁸F-fluorodeoxyglucose positron emission tomography
FEDAA1106
N-(5-fluoro-2-phenoxyphenyl)-N-(2-[(18F]fluoroethyl-5-
methoxybenzyl)acetamide
FFI
fatal familial insomnia
FIRDA
frontal intermittent rhythmic delta activity
FLAIR
fluid attenuated inversion recovery
fMRI
functional magnetic resonance imaging
FOXO
Forkhead box protein O
FP-CIT
N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl) nortropane
FROM-LP
Framework for Routine Outcome Measurement in Liaison Psychiatry
FSC
frontal-subcortical circuits
FTD
frontotemporal dementia
FTD-3
familial FTLD linked to chromosome 3
FTD-ALS
frontotemporal dementia-lateral sclerosis
FTD-FUS
frontotemporal dementia-fused in sarcoma protein
FTD-MND
FTD associated with motor neuron disease
FTD-UPS
frontotemporal dementia-ubiquitin-proteasome system
FTLD
frontotemporal lobar degeneration
FTLD-ni
FTLD-no inclusions
FTLD-TDP
FTLD with TDP-43 pathology
FUS

Abbreviations

fused in sarcoma
FY1 and FY2
Foundation Years 1 and 2
g
gram
GABA
 γ -aminobutyric acid
GAD
generalized anxiety disorder
GAD
Global Alzheimer's Disease Foundation
GAF
general assessment of functioning
GAP
Global Alzheimer's Platform
GAS
Geriatric Anxiety Scale
GBA
glucocerebrosidase
GBSC
Global Biomarkers Standardization Consortium
GCI
glial cytoplasmic inclusion
Gd
Gadolinium
GDS
Geriatric Depression Scale
GFR
glomerular filtration rate
GGR
global genome repair
GGT
globular glial tauopathy
Glx
glutamate/glutamine
GMS
General Medical Services
GMS
Geriatric Mental State
GP
general practitioner
GRE
gradient-recalled echo
GRN
Progranulin
GSF
Gold Standards Framework
GSS
Gerstmann-Sträussler-Scheinker syndrome

Abbreviations

GVD	granulovacuolar degeneration
GWAS	genome-wide association studies
h	hour
H/E	haematoxylin and eosin
HAM-D	Hamilton Depression Rating Scale (see also HDRS)
HAP	high-abundance protein
HAS	History and Aetiology Schedule
HbA1C	glycosylated haemoglobin
HCHWA-D	hereditary cerebral haemorrhage with amyloidosis-Dutch type
HCHWA-I	hereditary cerebral haemorrhage with amyloidosis of Icelandic type
HDL	high-density lipoprotein
HDRS	Hamilton Depression Rating Scale
HELP	Hospital Elder Life Program
HERNS	Hereditary endotheliopathy with retinopathy, nephropathy, and stroke
HIC	high-income country
HIV	human immunodeficiency virus
HM	healthcare management
HMPAO	hexamethylpropyleneamine oxime
hn-RNP	heterogenous nuclear ribonucleoprotein
HOPES	Helping Older People Experience Success
HPA	hypothalamic-pituitary-adrenal
HR	hazard ratio
HR-QoL	Health-related quality of life
HS	hippocampal sclerosis
HS-ageing	

Abbreviations

hippocampal sclerosis with advanced age
HS-CVD
hippocampal sclerosis with cerebrovascular diseases
HS-FTD
hippocampal sclerosis with non-tauopathy frontotemporal dementia
HS-SZ
hippocampal sclerosis with seizures
HS-tau
hippocampal sclerosis with tauopathies
HSV
herpes simplex virus
HTA-SADD
Health Technology Assessment Study of the Use of Antidepressants for
Depression in Dementia
HTRA1
HtrA serine peptidase/protease 1
HUPO
Human Proteome Organization
HUPO BPP
HUPO Brain Proteome Project
Hz
Hertz
IADL
instrumental activities of daily living
IAPT
Improving Access to Psychological Therapies
ICA
independent components analysis
ICD
International Classification of Diseases
ICH
intracerebral lobar haemorrhage
ICSD-3
International Classification of Sleep Disorder, 3rd Edition
ID
intellectual disability
IDE
insulin-degrading enzyme
IFCC-WG-CSF
International Federation of Clinical Chemistry and Laboratory
Medicine Working Group for CSF Proteins
IgG
immunoglobulin G
IgM
immunoglobulin M
IHD
ischemic heart disease
IIS
insulin/insulin-like growth factor signalling

Abbreviations

IL
interleukin
ILSA
Italian Longitudinal Study of Ageing
IMCA
Independent Mental Capacity Advocate
INPEA
International Network for the Prevention of Elder Abuse
Iodo-QNB
Iodo-quinuclidinylbenzilate
ipRGC
intrinsically photosensitive retinal ganglion cell
IPT
interpersonal therapy
IRR
incidence rate ratio
ISBD
International Society for Bipolar Disorder
ISF
individual service fund
ISS
International Study of Schizophrenia
ISTAART
International Society to Advance Alzheimer's Research and Treatment
IVD
in vitro diagnostics
IWG
International Working Group
JDR
Join Dementia Research
KAMA
Knowledge and Management of Elder Abuse
K-BIT
Kaufman Brief Intelligence Test
KICA
Kimberley Indigenous Cognitive Assessment
LACS
lacunar stroke
LAP
low-abundance protein
LASA
Longitudinal Ageing Study Amsterdam
LB
Lewy body
LBCRS
Lewy body composite risk score
LBD
Lewy body diseases; Lewy body dementia
LCP

Abbreviations

Liverpool Care Pathway
LE
limbic encephalitis
LFT
liver function test
LGI-1
leucine-rich, glioma-inactivated protein 1
LIC
low-income country
LLD
late life depression
LMIC
low- and middle-income country
LN
Lewy neurite
lncRNA
long non-coding RNA
LOAD
late-onset Alzheimer's disease
LOD
late-onset depression
LOMEDS
Late Onset Myoclonic Epilepsy in Down's Syndrome
LOS
late-onset schizophrenia
LP
lumbar puncture
LPA
lasting power of attorney
LPA
Logopenic aphasia
LPR
lipoprotein receptor-related protein
LPS
lipopolysaccharide
LSD
lysergic acid diethylamine
LSNS
Lubben Social Network Scale
LUTS
lower urinary tract symptoms
lvPPA
logopenic variant PPA
m
metre
MAC
membrane attack complex
MacCAT-T
MacArthur Competence Assessment Tool for Treatment

Abbreviations

MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	monoamine oxidase inhibitors
MAP	mitogen-activated protein; microtubule-associated protein; multi-analyte profile
MAPK	mitogen-activated protein kinase
MAPT	microtubule-associated protein tau
MBI	mild behavioural impairment
MCA	middle cerebral artery
MCA	Mental Capacity Act
MCANI	Mental Capacity Act (Northern Ireland)
MCI	mild cognitive impairment
MCID	minimum clinical important difference
MCI-LB	MCI with Lewy body disease
MCV	mean corpuscular volume/mean cell volume
MD	mean diffusivity
MDD	major depressive disorder
MDO	mentally disordered offender
MDQ	mood disorder questionnaire
MDS	Minimum Data Set
MDT	multidisciplinary team
M-ECT	maintenance ECT
MEG	magnetoencephalography
MELAS	Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes
MET	motivational enhancement therapy
MH	

Abbreviations

mental health
MHC
major histocompatibility complex
MHF
Mental Health Foundation
mHTT
mutant huntingtin protein
MI
motivational interviewing
MI
myoinositol
MIBG
metaiodobenzylguanidine
min
minute(s)
miRNA
microRNA
ml
millilitre
MMSE
mini-mental state examination
MND
motor neuron disease
MoCA
Montreal Cognitive Assessment
MOTYB
Months of the Year Backwards
MP4A
N-[(11)C]methylpiperidin-4-yl acetate
MRCPsych
examination for Membership of Royal College of Psychiatrists
MRI
magnetic resonance imaging
mRNA
messenger RNA
MRS
magnetic resonance spectroscopy
MSA
multiple system atrophy
MSNAP
Memory Services National Accreditation Programme
MSR
macrophage scavenger receptor
MSU
mid-stream specimen of urine
MTA
medial temporal atrophy
MTL
medial temporal lobe

Abbreviations

mTOR
mammalian target of rapamycin
MVC
motor vehicle crash
NAA
Narcotics Anonymous
NAA
N-acetylaspartate
NCD
neurocognitive disorder
NCEP ATP III
National Cholesterol Education Program Adult Treatment Panel III
NCI
neuronal cytoplasmic inclusion
NCS-R
US National Comorbidity Study Replication
NDSHS
Australian National Drug Strategy Household Survey
NER
nucleotide excision repair
NESARC
US National Epidemiologic Survey on Alcohol and Related Conditions
NFL
Neurofilament light chain
NFT
neurofibrillary tangle
NFTD
neurofibrillary tangle dominant dementia
nfvPPA
nonfluent or agrammatic variant PPA
NGS
next-generation sequencing
NHS
National Health Service
NIA-AA
National Institute on Aging and the Alzheimer's Association
NIA-RI
National Institute of Aging Nancy and Ronald Reagan Institute
NICE
National Institute for Health and Care Excellence
NIFID
neuronal intermediate filament inclusion disease
NIFID
neurofilament inclusion body disease
NIHR
National Institute of Health Research
NII
neuronal intranuclear inclusion
NINCDS-ADRDA

Abbreviations

National Institute of Neurological and Communicative Disorders and
Stroke-Alzheimer's Disease and Related Disorders Association
NINDS-AIREN
National Institute of Neurological Disorders and Stroke and
Association Internationale pour la Recherche et l'Enseignement en
Neurosciences
NLW
national living wage
NMDA
N-methyl-D-aspartate
NMS
neuroleptic malignant syndrome
NO
nitric oxide
NOAC
non-vitamin K oral anticoagulant
NP
neuritic plaque
NPI
neuropsychic inventory
NPV
net present value
NREM
non-REM
NSFs
National Service Frameworks
NSMHWB
Australian National Survey of Mental Health and Wellbeing
NT
neuropil thread
NTP
 α -, β -, and γ -nucleoside triphosphate
nv-PPA
non-fluent PPA
OABD
older-age bipolar disorder
OCD
obsessive-compulsive disorder
OFC
orbitofrontal cortex
OPCS
Office of Population Censuses and Surveys
OR
odds ratio
OSA
obstructive sleep apnoea
OSLA
Observational Scale of Arousal
OT

Abbreviations

occupational therapist
OTE
openness to experience
PA
psychological autopsy
PACS
partial anterior circulation stroke
PACSLAC
Pain Assessment Checklist for Seniors with Limited Ability to Communicate
PAINAD
Pain Assessment in Advanced Dementia
PAL
Paired Associates Learning
PALS
Patient Advice and Liaison Service
PAOS
pure progressive apraxia of speech
PART
primary age-related tauopathy
PATH
Problem Adaptation Therapy
PBS
positive behaviour support
PCA
posterior cortical atrophy
PCFT
Prudhoe Cognitive Function Test
PCr
phosphocreatine
PD
Parkinson's disease
PDB
Paget's disease of bone
PDD
Parkinson's disease dementia
PDE
phosphodiester
PDMCI
MCI in Parkinson's disease
PDNC
PD and normal cognition
PEACE
Palliative Excellence in Alzheimer Care Effort
PEDAL
Programa de Entrenamiento de Aptitudes para Latinos
PEG
percutaneous endoscopic gastrostomy
PET

Abbreviations

positron emission tomography
PET-PiB
positron emission tomography with Pittsburgh Compound B
P-gp
P-glycoprotein
pH
pondus hydrogenii
PHF
paired helical filament
Pi
inorganic phosphate
PiB
Pittsburgh compound B
PICALM
phosphatidylinositol binding clathrin assembly protein, involved in endocytosis
PiD
Pick's disease
PKA
protein kinase A
PLAN
Psychiatric Liaison Accreditation Network
PLD3
phospholipase D member 3
PLMS
periodic limb movements of sleep
PME
phosphomonoester
PNFA
progressive non-fluent aphasia
POA
power of attorney
POCS
posterior circulation stroke
POD
psychosis of dementia
POMH-UK
Prescribing Observatory for Mental Health
PORT
Patient Outcomes Research Team
PPA
primary progressive aphasia
PRNP
prion protein gene
PrP
prion protein
PS
Perry syndrome
PSP

Abbreviations

progressive supranuclear palsy
PST
problem-solving therapy
PSWC
periodic sharp wave complexes
p-tau
hyperphosphorylated tau at threonine 181
PTSD
post-traumatic stress disorder
PVI
perivascular astrocytic inclusion
PWD
person with dementia
QALY
quality-adjusted life year
QEEG
quantitative EEG
QoL
quality of life
RAGE
receptor for advanced glycation end products
RAVLT
Rey Auditory Verbal Learning Test
RBD
rapid eye movement sleep behaviour disorder
RCT
randomized controlled trial
REM
rapid eye movement
RLS
restless legs syndrome
RMT
reminiscence therapy
RNA
ribonucleic acid
RO
reality orientation
ROC
receiver operating characteristic
ROI
region of interest
ROS
reactive oxygen species
RR
relative risk
rs-fMRI
resting state functional magnetic resonance imaging
RSWA
REM sleep without atonia

Abbreviations

RTLA	right temporal lobe atrophy
rTMS	repetitive transcranial magnetic stimulation
RT-QuIC	real-time quaking-induced conversion
SAD	seasonal affective disorder
SALT	speech and language therapist
SAMD	senescence-associated mitochondrial dysfunction
sAPP	soluble ectodomain of APP
SARI	serotonin antagonist and reuptake inhibitor
SARS	severe acute respiratory syndrome
SASP	senescence-associated secretory phenotype
SAST	Short Anxiety Screening Test
SBP	systolic blood pressure
SBRT	Severe Behaviour Response Teams
SCA-17	spinocerebellar ataxia type 17
SCD	subjective cognitive decline
sCJD	sporadic Creutzfeldt-Jakob disease
SCLC	small cell lung cancer
SCN	suprachiasmatic nucleus
SD	standard deviation
SD	semantic dementia
SDB	sleep-disordered breathing
SE	supported employment
SERM	selective oestrogen receptor modulator
SF-36	36-item Short Form Health Survey
SIB	

Abbreviations

Severe Impairment Battery
SiP
Senses in Practice
siRNA
small interfering RNA
SIRT
sirtuin
SMC
Subjective Memory Complaint
SMI
severe mental illness
sMMSE
standardized MMSE score
SNAP
suspected non-Alzheimer's disease pathology
snoRNA
small nucleolar RNA
SNP
single-nucleotide polymorphism
SNRIs
selective serotonin and noradrenaline reuptake inhibitors
SOC
Selective Optimization with Compensation
SP
senile amyloid plaques
SPECT
single-photon emission computed tomography
SPMSQ
Short Portable Mental Status Questionnaire
SQiD
Single Question in Delirium
SQSTM1
p62/sequestome1
SQUID
superconducting quantum interference device
SRH
self-rated health
SSRI
selective serotonin reuptake inhibitors
ST
skills training
ST4, ST5, ST6
Specialist Training Years 4-6
STI
sexually transmitted infection
SUVr
standardized uptake value ratio
SVD
small vessel disease

Abbreviations

sv-PPA
semantic variant PPA
SWI
susceptibility-weighted imaging
TACS
total anterior circulation stroke
TAR
transactivation-responsive
TARDBP/TARDP
Transactive response DNA-binding protein 43
TBK1
TANK-binding kinase 1
TBP
TATA box-binding protein
TBSS
tract-based spatial statistics
TCR
transcription-coupled repair
TD
tardive dyskinesia
TD
topographical disorientation
tDCS
transcranial direct cortical stimulation
TDP-43
transactivation-responsive DNA-binding protein 43
TE
echo time
TFT
thyroid function test
tg
transgenic
THK5117
6-(3-18Fluoro-2-hydroxypropoxy)-2-(4-methylaminophenyl)quinoline
THK5351
(S)-6-(3-18Fluoro-2-hydroxypropoxy)-2-(N-methyl-2-aminopyridin-5-yl)quinoline
TM2D3
TM2 domain containing 3
TMEM106B
Transmembrane protein 106B
TMS
transcranial magnetic stimulation
TNF
tumour necrosis factor
TR
repetition time
TRAP

Abbreviations

tremor at rest, rigidity, akinesia (or bradykinesia), and postural instability
TREM2
triggering receptor expressed on myeloid cells 2
TSE
transmissible spongiform encephalopathy
TSI
Test for Severe Impairment
TSPO
translocator protein
t-tau
total tau
TYM
Test Your Memory
TYM-MCI
Test Your Memory for Mild Cognitive Impairment
Type I error
false positive error
Type II error
false negative error
U&Es
urea and electrolytes
UBQLN2
Ubiquilin 2
UNC5C
unc-5 homolog C
UPS
ubiquitin/proteasome system
UPS
Ubiquitin-positive
US
unconditioned stimulus
VaD
Veterans Administration
VaD
vascular dementia
VASS
Vulnerability to Abuse Screening Scale
VBA
voxel-based analysis
VBM
voxel-based morphometry
VBR
ventricle-to-brain ratio
VCI
vascular cognitive impairment
VCING
Vascular Cognitive Impairment Neuropathology Guidelines
vCJD

Abbreviations

variant Creutzfeldt-Jakob disease
VCP
valosin-containing protein
VD
vascular dementia
VEPs
visual evoked potentials
VGKC
voltage gated potassium channel
VLOSLP
very-late-onset schizophrenia-like psychosis
VLPO
ventrolateral preoptic nucleus
VP
ventriculoperitoneal
VRF
vascular risk factor
VT
validation therapy
WAIS-R
Wechsler Adult Intelligence Scale-Revised
WAY-100635
N-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamide
WHELD
Improving Wellbeing and Health for People with Dementia
WHIMS
Women's Health Initiative Memory Study
WHO
World Health Organization
WMH
white matter hyperintensity
WML
white matter lesion
WPBAs
Work Place Based Assessments
YLD
years lost due to disability
YLL
years of life lost
YMRS
Young Mania Rating Scale



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Biological aspects of human ageing

Chapter: Biological aspects of human ageing

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Introduction

The persistence of childhood memories in the mind of a centenarian is evidence enough of the remarkable durability of the brain at the tissue, cellular, and molecular levels, but it is beyond dispute that the brain of the most cognitively favoured centenarian will have suffered structural decline. For organisms in possession of a nervous system, such decline does not appear to be inevitable; though its nervous system is undoubtedly simpler, the freshwater cnidarian *Hydra* is able to escape such decline and, barring misfortune, is potentially immortal (Martinez, 1998). What separates *Hydra* from more familiar metazoans is not the simplicity of its nervous system, but rather its departure from the scheme of having specialized germline versus somatic cells. If (as in *Hydra*) all our cells had the qualities of multipotent stem cells, there would be no need for regenerative medicine. In humans, most cells (including neurons) are terminally differentiated somatic cells. Stem cells are rare, and for reproductive success, only the germ cells must be kept in pristine

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condition. Kirkwood's 'disposable soma' theory posits that, with only finite resources available to an organism, there must be a trade-off between the resources allocated to reproduction and the resources allocated to repair (Kirkwood, 1977). Any reduction in repair will be accompanied by the accumulation of molecular damage, and it is the accumulation of damage that drives ageing (Fig. 1.1). The inherent stochasticity of damage is sufficient to explain the lack of uniformity in ageing in genetically identical organisms (discussed in Kirkwood, 2008), and the inevitability of decline in the face of unrepaired molecular damage precludes the requirement for any programme 'for' ageing (other arguments have been marshalled towards the conclusion that no such programme is required or indeed has been demonstrated (Kirkwood and Melov, 2011)).

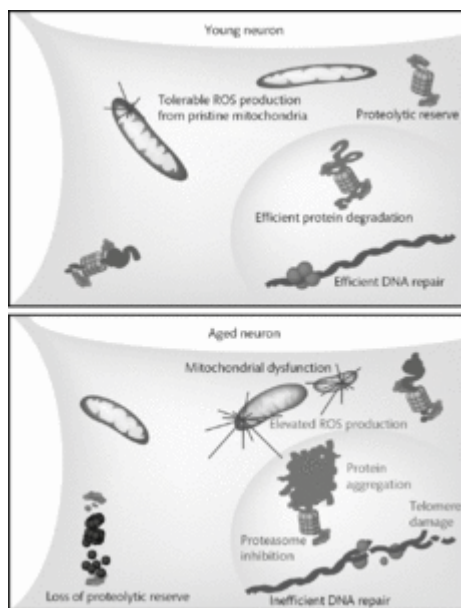


Fig. 1.1

Molecular damage affects multiple systems in ageing neurons.

The structural decline of the brain that is a hallmark of human ageing arises from unrepaired stochastic damage to its components, and it is the purpose of this chapter to deal with such damage at the molecular and cellular levels. It is widely accepted that the source of much damage in the ageing brain is reactive oxygen species (ROS), a collective term for oxygen radicals and other entities that cause oxidative damage (Halliwell, 2006). There is no escaping ROS—it constitutes a necessary by-product of cellular metabolism and a necessary intermediate of a number of cell signalling cascades (Nathan, 2003). Because of its energy demands, the brain is a voracious consumer of oxygen and a prodigious producer of ROS. The brain contains sufficient quantities of metal ions (notably those of iron) to ensure the production of reactive hydroxyl anions through Fenton chemistry (the thermodynamically favoured process which,

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through oxidation of metal ions, promotes the decomposition of hydrogen peroxide into hydroxyl anions and hydroxyl radicals) and, in addition, contains high levels of neurotransmitters such as dopamine, norepinephrine, and serotonin whose metal ion-catalysed oxidation can promote a vicious cycle of toxicity and further ROS release (Halliwell, 2006). The damage to biological molecules by ROS is not discriminating and will affect proteins, nucleic acids, carbohydrates, and lipids. Without discounting the importance of other molecular targets of ROS damage, the emphasis of the current chapter will primarily be on proteins and DNA, and the organelles and pathways most dependent on the continued integrity of these molecules (Fig. 1.2).

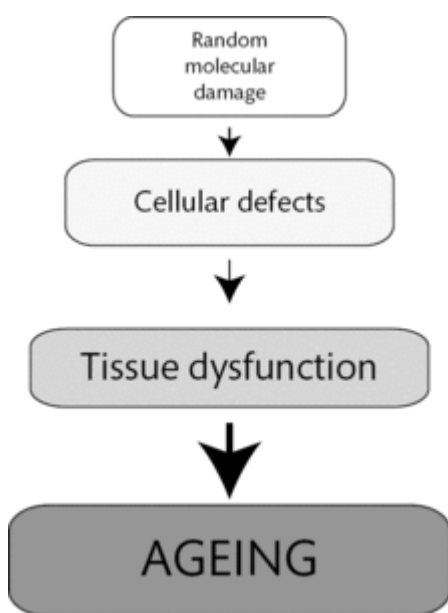


Fig. 1.2
Molecular damage underlies ageing.

Molecular aspects of ageing in the brain

Protein damage

To appreciate the consequences of oxidative damage to proteins and DNA within the ageing brain, one must first consider the very different fates of these entities. For the most part, proteins have limited half-lives and are constantly being replaced (an interesting exception being crystallin proteins within the lens; lens crystallins are permanent and, as such, can be used for accurate carbon-dating of individuals born during the era of atmospheric atomic tests!) (Lynnerup et al., 2008). DNA, on the other hand, must persist for the lifetime of the cell (temporarily leaving aside the more specialized case of mitochondrial DNA (mtDNA)). Though neurons, being post-mitotic, do not require pristine templates for DNA replicative purposes, the integrity of the genome is required for their

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active programme of ongoing transcription. It is therefore not surprising that damaged proteins are generally eliminated from mammalian cells (again, excepting damaged lens crystallins, whose destiny is the lens cataract), whereas damaged nuclear DNA is actively repaired.

There exist two cellular systems for the degradation of proteins, one involving membrane-bound vesicular trafficking of substrates and the other providing access to substrates throughout the cytoplasm and nucleus. The autophagic system is reliant on the engulfment of cellular components into membrane-delimited compartments which, upon fusion with lysosomes, become autophagosomes. Through autophagy, substrates are typically degraded on a timescale of hours, but the system has the capacity to process entire organelles (oxidatively damaged mitochondria, for example) and degrade all of the macromolecules therein. The ubiquitin/proteasome system (UPS), on the other hand, is a more specialized system for the degradation of proteins and, without the requirement for membrane trafficking, can operate on a much more rapid timescale. The UPS has remarkable specificity, discriminating between short-lived and long-lived proteins, post-translationally modified versus unmodified proteins, and normally structured versus aberrant and/or damaged proteins. This specificity is mediated by more than a thousand ubiquitin ligase (E3) enzymes that, in concert with a lesser number of ubiquitin-conjugating (E2) enzymes, associate with particular proteins and assemble upon them a chain of ubiquitin proteins (Hochstrasser, 1996). Once the chain reaches a threshold length of four ubiquitin monomers, the chain has physical affinity for subunits of the 26S proteasome (Piotrowski et al., 1997), and delivery of the substrate to this degradation machine results in its proteolytic destruction.

The hallmark of age-related neurodegenerative diseases is the appearance of protein conglomerates within the cytoplasm or nucleus of neurons and, in some cases, glia. These entities are of sufficient size to be visible by light microscopy and, in general, are designated inclusion bodies (Woulfe, 2007), though more specific designations may be associated with particular diseases (for example, the Lewy body in Parkinson's disease (PD) and Lewy body dementia). The composition of the inclusion body may vary from one neuropathological state to the next, but there is often a major constituent that typifies the disease and is its aetiological agent (for example, α -synuclein in the case of the Lewy body (Eriksen et al., 2003)). Most inclusion bodies are immunoreactive for ubiquitin, which may signify the failure of the UPS to eliminate their constituent proteins (Gray et al., 2003). Indeed, the most parsimonious explanation for inclusion bodies is the passive agglomeration of aberrant proteins which, as a result of damage or misfolding, expose hydrophobic regions that would normally be concealed within structural folds. While this may be true for nuclear inclusions, the situation in the cytoplasm may be more complex. There is evidence that proteins are actively transported along microtubules to aggresomes (cytoplasmic inclusions assembled in the vicinity of the centriole) (Johnston et al., 1998). It has been suggested

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that Lewy bodies may represent a form of aggresome (McNaught et al., 2002), though the behaviour and composition of aggresomes in cell culture models are not in complete agreement with findings from autopsy specimens (Waxman et al., 2009), and questions remain about the relationship of these entities.

Inclusion bodies can be detected in the brains of normal aged individuals (those not diagnosed with neurodegenerative disease), and it is reasonable to suggest that their presence denotes the age-related decline of proteolytic efficiency. Examples of such inclusions would include the rod-like and skein-like inclusions of the aged neostriatum, the granular cytoplasmic inclusions of the inferior olivary nucleus, and the colloid or hyaline inclusions of the hypoglossal and spinal motor neurons of the elderly (discussed in Gray et al., 2003). Though the protein constituents of these inclusions are at present poorly characterized, their age-related deposition points to the existence of a 'tipping point', beyond which the rate of accumulation of abnormal protein exceeds the capacity for its elimination, resulting in widespread protein aggregation and the ultimate accretion of aggregates into inclusion bodies. In the absence of heritable DNA mutations, the source of the abnormal protein would be stochastic damage and misfolding from intrinsic ROS production or ROS from environmental sources, coupled with the incessant production of misfolded protein from translational and post-translational errors (accounting for as much as a third of total protein production by some estimates (Schubert et al., 2000)). In the disease state, inclusions would occur precociously due to the added burden of abnormal protein, either genetically encoded or of idiopathic origin. The tipping point conjecture is surely consistent with the observation that the symptoms of pernicious inherited diseases (Huntington's disease, for example) do not become apparent until adulthood is attained, and often not until late in life. The correlation (Gusella and MacDonald, 2006) between disease onset in Huntington's disease and the length of the expanded polyglutamine tract in the affected protein also fits with the tipping point conjecture; the longer the repeat, the greater the burden to the UPS and the earlier it is likely to be overwhelmed. The greater prevalence of inclusions within neurons, as opposed to glia, of Huntington's disease patients is also in agreement with the conjecture or is at least in agreement with findings from cell culture model systems of these cell types. UPS activity was found to be lower in cultured mouse neurons than in cultured glia and shows a more pronounced age-related decline (Tydlacka et al., 2008). Mutant huntingtin protein was efficiently degraded in cultured glia unless proteasome activity was pharmacologically inhibited (Tydlacka et al., 2008).

The functional basis of UPS decline in ageing individuals has yet to be fully elucidated. That UPS efficiency does decline is evident from the accumulation of UPS substrates in mouse brain lysates, typically visualized by probing western blots of such samples with an antibody specific for ubiquitin. What is observed is an age-dependent increase in

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the intensity of a high-molecular weight smear (Gray et al., 2003; Ohtsuka et al., 1995), also observed in the brain of human Huntington's disease patients and mouse models thereof (Bennett et al., 2007). This smear arises from ubiquitin chains linked to a range of protein substrates (Bennett et al., 2007). The proteolytic deficit that generates this backlog of undigested UPS substrates could arise from the age-related decline in the expression of some key UPS component or components, and microarray studies (Blalock et al., 2003; Lee et al., 2000) have identified candidate UPS components whose levels were decreased in aged mouse brains (at least at the RNA level). Proteasome activity has been shown to decline in the ageing brain (Keller et al., 2002), but this decline has not been strongly correlated with a reduction of any of the proteasome subunits and may reflect damage to the proteasome, rather than the loss of expression.

The prospect of proteasome damage raises an interesting 'chicken and egg' problem. Does a growing burden of protein damage within the brain ultimately overwhelm the capacity of the proteasome, or does age-related damage to the proteasome itself (from ROS or other sources) eventually generate the backlog of undigested substrates? It is conceivable, perhaps likely, that a vicious cycle of inhibitions exists, and regardless of the entry point, the outcome will be deleterious for the cells in which the vicious cycle occurs (Fig. 1.3). Support for such an inhibitory cycle comes from time lapse imaging and stochastic computer modelling of cells expressing aggregation-prone proteins (Tang et al., 2010), wherein reciprocal inhibition is apparently mediated by ROS. This study also highlighted the importance of the stress-activated p38 mitogen-activated protein (MAP) kinase (MAPK) molecule in mediating the death of inclusion-bearing cells. Because it can be activated by oxidative conditions (via the redox-sensitive upstream ASK1 kinase) (Matsuzawa and Ichijo, 2008), p38 MAPK would be responsive to the operation of the proposed vicious cycle, and in the experimental system, cell survival can be enhanced by pharmacological or genetic inhibition of p38 (Tang et al., 2010), but not other MAPKs (Tsirigotis et al., 2008).

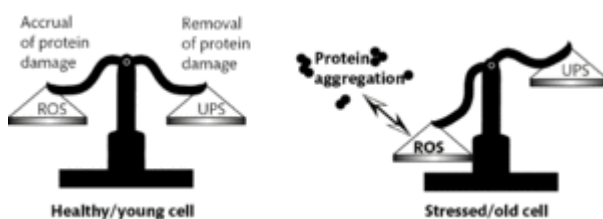


Fig. 1.3

Loss of balance in protein homeostasis typifies ageing at the cellular level.

For purely physical reasons, the formation of an inclusion body would seem a potentially catastrophic event, and the long association of

Biological aspects of human ageing

inclusion bodies with neuropathological conditions has cast them in an understandably negative light, but there is a body of work that would argue the converse—under some conditions, inclusion body formation appears to correlate with neuronal survival. The best evidence for the neuroprotective effect of inclusions comes from live cell imaging of neurons made to express fluorescent versions of an aggregation-prone protein. In these experiments, it is possible to track the fate of individual cells and, in so doing, to document the enhanced survival of neurons that formed inclusions early (Arrasate et al., 2004). The supposition (now widely accepted) is that smaller-order aggregates (oligomers) are the more toxic entities, perhaps because of their propensity to bind promiscuously to essential cellular proteins. By sequestering such dangerous entities into inclusions, their potential for promiscuous interactions is diminished and neuroprotection is hence conferred. While the beneficial effect of inclusions in the cell culture model system is indisputable, the time frame of such experiments is necessarily short and may not reflect the fate of neurons laden with inclusions *in situ*. Inclusions are known to concentrate iron and may serve as centres of Fenton-mediated ROS production (Firdaus et al., 2006). The long-term effects of localized ROS production around inclusions are unlikely to be beneficial.

A final, rather terrifying aspect of the aberrant proteins and protein aggregates that accumulate in the ageing brain is their potential to spread to adjacent and/or distant cells and wreak havoc in a prion-like manner. The spreading or ‘seeding’ of protein aggregates has been the subject of great interest and has been discussed in the context of a growing list of aggregation-prone proteins, including β -amyloid, α -synuclein, tau, huntingtin, superoxide dismutase, fused in sarcoma (FUS), and transactivation-responsive (TAR) DNA-binding protein 43 (TDP-43) (Brundin et al., 2011; Dunning et al., 2012; Jucker and Walker, 2011; Polymenidou and Cleveland, 2011). Aggregates may be actively secreted through exocytosis into the extracellular milieu or within membrane-delimited exosomes that could travel through the vasculature to distant sites. Aggregates may also be released passively during cell death and be taken up by endocytic pathways of nearby cells, or may travel through tunnelling nanotubes to access adjacent cells, as has been documented for prions (Gousset et al., 2009). Aggregate seeding has been proposed as a possible mechanism for the propagation of pathology in a number of age-related conditions in which localized neurodegeneration becomes more widespread. In Alzheimer’s disease (AD), the tau tangles stereotypically occur first in the locus caeruleus and transentorhinal area, then spread to the amygdala and connected cortical regions (Braak and Braak, 1991). In PD, though not in all Lewy body diseases, there may be a spread of pathology through anatomically connected regions of the brainstem, limbic system, and neocortex, but it has been hypothesized that this pathology is preceded by degenerative changes in olfactory structures and the enteric plexus, perhaps due to exposure of these tissues to an environmental agent such as a virus (Jang et al., 2009). If

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with ageing, there is a relentless loss of protein-degradative capacity, as described earlier, it would follow that the aggregate 'seeds' would find increasingly fertile soil in the neurons of the aged brain.

DNA damage

It is beyond the scope of this chapter to summarize the extensive literature on age-related damage to the DNA genome (a subject that merits book-length treatment on its own (Vijg, 2007)), but the extensive reliance of DNA repair systems on ubiquitin-mediated proteolysis leads to the necessary conclusion that age-related decline of the latter will ultimately compromise the former. Ubiquitin is employed in some forms of DNA repair in a non-proteolytic role as a scaffold or molecular switch (Chiu et al., 2006), but in post-mitotic cells such as neurons, it is the proteolytic function of the UPS in nucleotide excision repair (NER) that is of paramount importance (Nospikel, 2011). In particular, it is the transcription-coupled repair (TCR) system, a subsystem of NER, that is of greatest relevance. TCR is charged with maintaining the integrity of the transcribed strand of DNA; for metabolically active cells such as neurons, a lesion within a coding region can block transcription, with disastrous consequences, and such lesions must be detected and rapidly repaired. A second form of NER (global genome repair, or GGR) maintains genomic integrity at sites throughout the genome but, for post-mitotic cells, is much less critical. The TCR and GGR pathways have shared components and components that are unique, but both sense distortions of the double helix and ultimately utilize common ubiquitin-mediated degradation machinery (based on cullin 4A complexes) to remove multicomponent repair systems from the repaired lesion. As a last resort, stalled RNA polymerase II can itself be degraded by the ubiquitination machinery of the TCR system to 'reboot' gene transcription. The importance of TCR to neuronal homeostasis was suggested by the neuronal deficits of individuals bearing mutations in TCR-related genes, and has been confirmed experimentally by the age-related neurodegenerative phenotypes of mice engineered to be deficient in TCR components (Jaarsma et al., 2011). As the efficiency of ubiquitin-mediated proteolysis declines, so too should the efficiency of TCR. Should TCR efficiency fall below a critical threshold, the subsequent shutdown of transcription could only imperil the functioning of the ageing brain.

Ageing at the cellular and systems level

Genetics and epigenetics

There is strong evidence for the role of genetics in age-related diseases, especially cardiovascular diseases, diabetes, AD, and PD (Ruse and Parker, 2001). A systematic review of published family, twin, linkage, and association studies found evidence for the role of several genes in successful ageing (Glatt et al., 2007). These genes included *APOE*, *GSST1*, *IL6*, *IL10*, *PON1*, and *SIRT3*. The role of *APOE* in AD is well known. It exists as three different alleles: *APOE2*, *APOE3*, and *APOE4*,

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with the E4 isoform being the most recognized genetic risk factor for late-onset AD (Saunders et al., 1993). Conversely, the rarer E2 isoform is associated with a protective role (Corder et al., 1994), and the most frequent E3 isoform shows an intermediate effect in terms of both disease risk and age of onset. Many genome-wide association studies (GWAS) have been carried out for individual age-related diseases. However, a more effective approach has been recently demonstrated in which information from GWAS and candidate gene studies were combined to find allelic variants that simultaneously increase the risk of several age-related diseases (Kulminski et al., 2016).

There are many model systems to address the role of genetics in ageing, including nematode worms (*Caenorhabditis elegans*), fruit flies (*Drosophila melanogaster*), mouse, and yeast. These species are short-lived, and so it is feasible to measure the effects of different genetic strains on maximum and average lifespan. The first 'longevity gene' found in *C. elegans* was *AGE-1* (Friedman and Johnson, 1988), and since then approximately 750 genes have been discovered which affect lifespan in *C. elegans*. A set of genes which have attracted a lot of attention are those involved in an insulin-like signalling pathway and which regulate the activity of the transcription factor DAF-16. Genes involved in insulin signalling are also known to affect the lifespan of *D. melanogaster* and mice. In humans, a variant at the FOXO3A locus has been linked with longevity (reviewed in Martins et al., 2016). Other proteins and pathways that have been shown to have effects on ageing are the Sirtuins, the insulin/insulin-like growth factor signalling (IIS) pathway and the mammalian target of rapamycin (mTOR) pathway (reviewed in Pan and Finkel, 2017). For example, mutations that decrease TOR activity have been shown to extend lifespan in *C. elegans*, *D. melanogaster*, yeast, and mice (Jia et al., 2004; Kapahi et al., 2004; Powers et al., 2006; Selman et al., 2009).

Epigenetic alterations with age has recently been categorized as one of the hallmarks of ageing (López-Otín et al., 2013). Epigenetic mechanisms involve changes in gene expression which are not due to changes in the DNA sequence, but rather in gene regulatory mechanisms such as DNA methylation, histone deacetylation, and non-coding RNAs. Epigenetic changes are essential during development and differentiation but can also occur later in life in response to changes in the cellular environment or as a result of random errors. These changes are passed on when cells divide but are generally not passed on through the germ line. DNA methylation is the most studied epigenetic modification and is the subject of many reviews in the context of ageing (for example, Gravina and Vijg, 2010; Jones et al., 2015; Xiao et al., 2016). Approximately 40% of promoters in mammalian genes contain clusters of unmethylated CpG pairs, known as CpG islands. These islands are targets for transcription factors. During ageing, changes in methylation status of CpG islands occur which can lead to either hypermethylation or hypomethylation. Recently it has been shown in mice that DNA methylation of certain CpG sites may be a

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predictor of chronological age (Petkovich et al., 2017). In human ageing, epigenome-wide association studies (EWAS) have tried to identify an epigenetic clock whereby methylation changes at certain loci consistently change with age in different individuals. The CpG island of the gene *ELOVL2* is highly ranked as an age-differentially methylated region (a-DMR) in nearly all EWAS in a variety of tissues (reviewed in Bacalini et al., 2017). However, only a few a-DMRs have been associated with changes in gene expression, for example, *BDNF* and *SST* have lower gene expression in the orbital frontal cortex of older individuals (McKinney et al., 2015). Stochastic changes in methylation lead to a divergence of the epigenome with age, a phenomenon known as epigenetic drift, that is particularly evident in studies of monozygotic twins (for example, Fraga et al., 2005). A link between epigenetics and the senescence pathway (discussed in Cellular mechanisms of ageing) has received much attention in recent years (reviewed in Sidler et al., 2017). MicroRNAs (miRNAs) are short non-coding RNAs that interact with target genes by enhancing degradation or preventing translation of messenger RNA (mRNA). A comprehensive discussion of miRNAs in ageing is beyond the scope of this chapter, but we refer the interested reader to a recent comprehensive review (Williams et al., 2017) and to a brief discussion of the role of miRNAs in the ageing brain (Chapter 2).

Cellular mechanisms of ageing

Mitochondria

Mitochondria are the powerhouse of the cell, producing most of the cell's supply of adenosine triphosphate (ATP). They also produce ROS as a by-product of respiration, which can damage cellular components. Mitochondria are themselves particularly prone to damage since they are close to the source of ROS, and it has long been considered that mtDNA mutations contribute to ageing (Linnane et al., 1989). Mitochondria are very dynamic organelles and undergo turnover (independently of the cell cycle), fusion, fission, and movement through the cell. Movement of mitochondria is particularly important in neurons since they are required at synapses, and so they are continually transported from the cell body to axonal synapses (anterograde transport) and back again (retrograde transport) for degradation. There is evidence for impaired movement in age-related neurodegenerative diseases. A mouse model of Huntington's disease reported impairment in both anterograde and retrograde transport in cells in specific neurons which are known to be susceptible to cell death in the human disease (Her and Goldstein, 2008).

In AD, it has been shown that amyloid beta impairs anterograde transport, resulting in degeneration of synapses (Calkins and Reddy, 2011). Furthermore, the mitochondrial protein Pink1, which is mutated in some familial forms of PD, has been shown to play a role in mitochondrial transport (Weihofen et al., 2009). Mitochondria are degraded by lysosomes by a process known as mitophagy (mitochondrial autophagy). For many years, this was considered a random process, but there is

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increasing evidence that mitophagy is selective (reviewed by Wei et al., 2015). For example, it has been shown that Pink1 is recruited to mitochondria with Parkin (an E3 ubiquitin ligase), inducing mitophagy (Kawajiri et al., 2010) and a vesicular pathway to selectively remove damaged mitochondrial proteins (McLelland et al., 2014). The latter study showed that PD-associated Parkin mutants lost the ability to perform this role. Since lysosomal degradation pathways decrease in efficiency with age, there is also impaired degradation of mitochondria, which could lead to an increase in the levels of dysfunctional mitochondria. Degradation of mitochondria must be balanced by biogenesis of new mitochondria in order to maintain mitochondrial numbers, but this has been shown to be diminished with age (Fannin et al., 1999). In addition, PGC-1 α , an intracellular mediator of biogenesis, has been shown to be decreased in age-related diseases such as diabetes and neurodegeneration (reviewed by Wenz, 2011). Mitochondria form networks and continuously undergo fission and fusion whereby an individual mitochondrion either leaves or joins the network, respectively. The purpose of fission and fusion is still unclear, but the general consensus is that it allows exchange of mtDNA and mitochondrial proteins and helps to segregate damage prior to fission and degradation. In neurons, fission and fusion of mitochondria take place in the cell body and also along axons and has been widely studied using live cell imaging (Jahani-Asl et al., 2007; Twig et al., 2008). Disturbances in the balance of fission and fusion, resulting in abnormally long or short mitochondria, have been implicated in age-related neurodegeneration (Knott and Bossy-Wetzel, 2008).

The importance of mitochondria in ageing was highlighted in 1991 by the proposal of the mitochondrial theory of ageing (Miquel, 1991), an extension of the free radical theory (Harman, 1956), being based on the idea that ROS generated by mitochondria induce mutations in mtDNA which leads to more ROS, and a vicious cycle ensues. There is a wealth of evidence to support the mitochondrial theory of ageing. For example, studies have shown that an excess production of ROS leads to more mtDNA damage in human tissues (Cortopassi and Arnheim, 1990; Hayakawa et al., 1991; Hayakawa et al., 1992). Conversely, targeting catalase to mitochondria led to lower levels of mtDNA mutations and extended lifespan (Schriner et al., 2005). There is evidence for an accumulation of mtDNA mutations with age (Wallace, 1999). In particular, high levels of deleted mtDNA were found in substantia nigra neurons from both aged controls and individuals with PD (Bender et al., 2006; Kraytsberg et al., 2006). These mtDNA mutations are somatic, with different clonally expanded deletions in individual cells, and high levels of these mutations are associated with respiratory chain deficiency. Respiratory activity has been shown to be decreased with age in several human tissues, for example in the liver (Yen et al., 1989) and skeletal muscle (Conley et al., 2000; Trounce et al., 1989). In addition, it has been shown that accelerating the mtDNA mutation rate can result in premature ageing. For example, mice with a mutant *POLG*, the gene that encodes the only mtDNA polymerase, prematurely exhibited many

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phenotypes associated with human ageing and had shorter lifespan (Kujoth et al., 2005; Trifunovic et al., 2004). Age-related increases in the frequency of cytochrome c oxidase (COX)-deficient cells, which are associated with mtDNA mutation, have been reported in human muscle (Brierley et al., 1998; Muller-Hocker, 1989), brain (Cottrell et al., 2000; Cottrell et al., 2001), and gut (Taylor et al., 2003). Cells in which mtDNA mutation reaches a high level are likely to suffer from impaired ATP production, resulting in a decline in tissue bioenergenesis. However, there is also controversy about the role of mitochondrial damage in ageing and some studies in mice show that there is no effect of mitochondrial antioxidants on lifespan (reviewed by Jang and Remmen, 2009). Interestingly, although the *POLG* mice model demonstrated that an increase in mitochondrial mutations was associated with a variety of ageing phenotypes, the mice did not show any signs of increased oxidative stress (Trifunovic et al., 2005). This puts into question the idea that oxidative stress plays a major role in the ageing process. A study that counters the mitochondrial theory of ageing is a long-lived mouse, heterozygous for *CLK1* (CDC-like kinase 1), a mitochondrial enzyme necessary for ubiquinone biosynthesis, despite having massive mitochondrial dysfunction starting early in life (Lapointe and Hekimi, 2008). Therefore, the link between mitochondria and ageing is complex. In particular, mitochondria cannot be considered alone, as they affect many other cellular mechanisms. For example, a study suggests interplay between mitochondrial and proteasome activity in skin ageing (Koziel et al., 2011).

Telomeres

Telomeres are repetitive sequences of non-coding DNA that protect the ends of chromosomes from degradation and end-to-end fusions. In humans, telomeres end with a stretch of single-stranded DNA, known as G-overhangs which form a T-loop structure. This structure is bound and stabilized by proteins to form a so-called cap to distinguish it from a DNA break. Telomeres shorten with each cell division due to the end-replication problem (Olovnikov, 1971) and also oxidative stress which has been shown to accelerate telomere shortening by causing single-strand breaks in telomeric DNA (von Zglinicki, 2002). Further evidence for the role of oxidative stress is that the addition of antioxidants to cell cultures slows telomere shortening (Serra et al., 2003). Telomeres need a minimum length in order to maintain their capped structure; however, the exact threshold required is not known. Short uncapped telomeres are seen by the cell as DNA damage, leading to induction of the DNA damage response. This can result in permanent cell cycle arrest, also known as cellular or replicative senescence, which is discussed in more detail in Cellular senescence.

Telomerase is an enzyme that elongates telomeres. In humans, it is active in most embryonic tissues during early development. However, it is down-regulated during cellular differentiation in most somatic cells, apart from endothelial cells and some adult stem cells. Therefore, telomeres shorten

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with age in most human tissues and organs (Djojosebroto et al., 2003). Telomere shortening was not observed in the brain during ageing in a study which analysed whole-organ biopsies (Allsopp et al., 1995); however, this does not preclude the possibility that telomere shortening occurs during ageing in specific regions of the brain or that telomere shortening in other cell types affects brain function (Jiang et al., 2007). For example, patients with AD have abnormally short telomeres in lymphocytes, when compared to age-matched controls (Panossian et al., 2003).

A meta-analysis of telomere length in PD for eight published studies indicated that there is no consistent evidence of shorter telomeres in this disorder (Forero et al., 2016). However, a more recent study which was not included showed that telomeres of PD patients were shorter in buccal epithelial cells, but identical in blood cells, compared to age-matched controls (Kolyada et al., 2016).

Studies have investigated whether telomere length could be used as a biomarker of ageing and age-related diseases; however, it has been shown that data are inconsistent (reviewed in Sanders and Newman, 2013). More recently, an interesting study indicated that telomere length and the DNA methylation epigenetic clock are independently associated with chronological age (Marioni et al., 2016). To conclude, despite the inconclusive evidence so far, research into the role of telomere shortening in ageing continues, and with the advancement of new techniques, conclusive evidence of a correlation between telomere length and healthy ageing may be obtained in future (Sanders and Newman, 2013).

Cellular senescence

The fact that human fibroblast cells can only divide a limited number of times was first discovered by Leonard Hayflick and Paul Moorhead in the early 1960s (Hayflick and Moorhead, 1961). The maximum proliferative lifespan of cells is called the Hayflick limit, and the irreversible loss of division potential of somatic cells is known as replicative cellular senescence. Telomere shortening has long been thought to be the biological counter for replicative senescence. However, it is not telomere length per se that triggers cell arrest, but rather some property of the telomere such as uncapping (von Zglinicki, 2003). As well as replicative senescence, cells can also undergo telomere-independent senescence via the DNA damage response (d'Adda di Fagagna, 2008), protein damage (Castro et al., 2012), and mitochondria dysfunction (Miwa et al., 2014). Cellular senescence acts as a tumour suppressor mechanism (Bartek et al., 2007) and is also involved in tissue remodelling after an acute damaging event, after which the senescent cells are cleared by the immune system (reviewed in Childs et al., 2015). However, senescence which has been triggered by chronic stress contributes to a loss of tissue homeostasis in human ageing. This is evident by the increase in senescent cells with age in various tissues (Dimri et al., 1995; Farr et al., 2016; Jurk

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et al., 2012; Wang et al., 2009) and in age-related diseases (reviewed in Childs et al., 2015).

There is evidence for a link between mitochondrial dysfunction and senescence (reviewed in Korolchuk et al., 2017) and, in particular, a recent study showed that loss of mitochondrial sirtuins (SIRT6) induced senescence with a distinct senescent phenotype involving the NADP-AMPK-p53 pathway (Wiley et al., 2016). On the other hand, senescence induction of the DNA damage response contributes to mitochondrial dysfunction, known as senescence-associated mitochondrial dysfunction (SAMD), leading to higher ROS production through a signalling pathway involving p53, p21, p38, and TGF β (Passos et al., 2010). In addition, this study showed that ROS contribute in a stochastic manner to the long-term maintenance of DNA damage foci, leading to permanent cell cycle arrest.

Senescent cells have a detrimental effect on neighbouring cells and the surrounding extracellular matrix, a phenomenon known as the bystander effect. This has been demonstrated *in vitro* in senescent human fibroblasts, and possibly *in vivo* in mouse liver hepatocytes (Nelson et al., 2012). The bystander effect may be due to senescent cells secreting not only inflammatory cytokines and growth factors, termed the senescence-associated secretory phenotype (SASP), but also reactive species, such as ROS and nitric oxide (NO), which then diffuse into neighbouring cells and cause DNA damage (Sokolov et al., 2007). A recent study in MRC fibroblasts provided evidence that both SASP and SAMD are involved in the bystander effect (Nelson et al., 2017) by showing that the DNA damage response induces SAMD, which leads to a further increase in ROS, activation of SASP via NF κ B, and induction of DNA damage in bystander cells. However, they found that neither interleukin (IL)-6 nor IL-8 played a major role in the bystander effect and concluded that more work is needed to identify the signal transducers (Nelson et al., 2017). In view of the detrimental effects of senescence in ageing, there has been recent interest in the possible benefits of senolytics (drugs that selectively induce apoptosis of senescent cells). Studies have been carried out in mice (for example, Baar et al., 2017), but the potential for human health is not yet known.

Apoptosis

Apoptosis, or programmed cell death, is an essential process during development. Apoptosis is also required to remove damaged cells which can then be replaced by the division of healthy cells to maintain tissue homeostasis. The processes of cell death and proliferation need to be finely balanced. Too much cell death leads to loss of tissue and has been implicated in many age-related diseases such as neurodegenerative disorders, osteoporosis, and atherosclerosis. On the other hand, too much cell proliferation can lead to cancer. Apoptosis is highly regulated and can be activated by either intrinsic or extrinsic signals. The extrinsic pathway is triggered by extracellular signal proteins binding to cell membrane

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death receptors such as the tumour necrosis factor (TNF) receptor or the Fas death receptor. After binding, death receptors recruit intracellular adaptor proteins which, in turn, recruit procaspases, leading to a caspase cascade and finally cell death. There is evidence for altered caspase activity with ageing, which may contribute to dysregulation of the extrinsic pathway (Zhang et al., 2003). Cells can also activate apoptosis from signals within the cell such as DNA damage, lack of nutrients, or hypoxia. The intrinsic pathway requires the release of cytochrome c from mitochondria, which binds to Apaf-1 and procaspase-9 to form the apoptosome. This pathway can be triggered directly or indirectly by ROS, which may explain the increase in apoptosis with age (Simon et al., 2000). There are many proteins involved in regulating the intrinsic pathway, including Bcl-2, Bax, Jnk, p38MAPK, and p53, and all these are known to play a role in ageing. For example, Bcl-2 and Bax are anti- and pro-apoptotic factors, respectively, and their ratio determines cellular outcomes. Cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) upregulates Bcl-2 to promote cell survival, and it has been shown that CREB family members are critical for neuronal survival *in vivo* (Mantamadiotis et al., 2002). Many other pathways are involved, some of which are neuron-specific and are the subject of a recent review (Pfisterer and Khodosevich, 2017).

Age-related neurodegenerative diseases are associated with death of neurons in specific regions of the brain caused by too much apoptosis (Mattson, 2000). It has been shown that p53 is up-regulated in AD, which may contribute to the increase in apoptosis (Hooper et al., 2007). Since neurons are mostly post-mitotic, cells cannot be replenished and brain atrophy results. Skeletal muscle and heart are also post-mitotic tissues that are affected by age-related disturbances, leading to overactive apoptotic pathways (Pollack et al., 2002). On the other hand, cancer cells and senescent cells are resistant to apoptosis, so that they accumulate with age. In addition to apoptosis, other forms of cell death such as necrosis and overactive autophagy may contribute to ageing (reviewed in Tower, 2015).

Stochasticity

It has been observed that there is wide variation in lifespan in genetically identical organisms raised in a constant environment, which therefore must be due to random effects (Herndon et al., 2002; Kirkwood et al., 2005). Finch and Kirkwood (2000) proposed intrinsic chance as a third factor to the conventional two-factor model of ageing which attributes genetics and the environment as the main determinants of lifespan. The accumulation of molecular damage is random both in terms of when and where damage occurs. Chance events also occur in many other processes such as reproductive ageing, development, cell numbers, thresholds for dysfunction, cell fates, telomere shortening, and control of gene expression (Finch and Kirkwood, 2000). For example, it is known that there is large stochastic variation in telomere length (Martin-Ruiz et al.,

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2004), and epigenetic changes are also highly stochastic and have been shown to explain why identical twins age differently (Petronis, 2006).

Dietary restriction

Dietary restriction (DR) is the most robust intervention known to extend lifespan and reduce morbidity in a range of species, including rodents, *C. elegans*, *D. melanogaster*, and yeast. The extensions in lifespan are quite substantial. For example, a study showed that the average lifespan of mice in the top decile was 53 months in the group fed on a diet with a 35% reduction of the *ad libitum* intake, compared to 35 months for the control group (Weindruch et al., 1986). Another rodent study attributed an increase in lifespan of dietary-restricted animals to a reduction in age-related diseases such as diabetes, atherosclerosis, respiratory disease, and cancer (Fontana and Klein, 2007). On the other hand, DR studies in non-human primates have failed to show any clear effect on the ageing process per se, although there have been indications of health benefits, most probably associated with the fact that *ad libitum* feeding may have adverse effects on metabolic disorders (Selman, 2014).

DR does not necessarily involve a reduction in calories (as in calorie restriction) but includes other interventions such as restriction of specific macronutrients or intermittent fasting in which the overall calorie intake may or may not be reduced. Intermittent fasting, although not new, has recently received a lot of attention in terms of its benefits for healthy ageing. However, the evidence is not yet conclusive and requires further investigation (Patterson et al., 2015). The mechanisms underlying the beneficial effects of DR are not fully understood, but the general consensus is that metabolic pathways are involved with down-regulation of the IIS, TOR, and/or glucose protein kinase A (PKA) signalling pathways (reviewed by Santos et al., 2016). A recent study showed that DR protects against age-related changes in DNA methylation (Hahn et al., 2017), and calorie restriction has also been shown to affect the circadian cycle (for example, Patel et al., 2016), indicating that many interrelated mechanisms are involved.

Systems biology

The reader may rightly conclude that ageing is very complex and involves multiple mechanisms. The overlap between mechanisms is very evident from the previous sections. For example, mitochondrial dysfunction has an impact on all energy-dependent cellular mechanisms. While reductionist approaches have predominated in the past, the realization for the need of an integrative approach was recognized near the start of this century (von Zglinicki et al., 2001). Reductionist approaches are still required to generate detailed data, but the emphasis is now on integrating new findings with previous discoveries. In addition, powerful new technologies, such as functional genomics, produce large volumes of data that need sophisticated computer software packages for analysis. Therefore, a multi-disciplinary framework of systems biology is essential

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to advance our understanding of ageing (Kirkwood, 2011). Systems biology involves close interaction and collaboration between biologists, mathematicians, computer scientists, engineers, and statisticians. The emphasis is on an iterative cycle of experiment, theory, and quantitative modelling (Fig. 1.4).

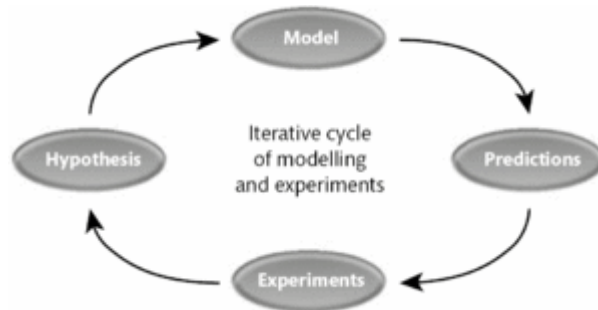


Fig. 1.4
An iterative cycle of modelling and experimentation.

Mathematical and computer modelling is now being increasingly used in biomedical research. However, many scientists are still unclear on the use of models in this area, and so we summarize the main advantages of using models as an additional research tool. Model building requires a specific hypothesis, and each element of the model and how it interacts with other elements must be specified. This often highlights unknown elements and uncertainties about specific reactions. In this case, more than one model can be built to investigate different possibilities. The model can be used to make both qualitative and quantitative predictions which may suggest further experiments. Modelling is relatively inexpensive and quick, compared to laboratory experiments, and so it can provide a low-cost rapid test-bed for candidate interventions.

A wide range of models have already been developed to investigate the molecular mechanisms of ageing (reviewed in Mc Auley et al., 2017) such as telomere erosion (Proctor and Kirkwood, 2002 and 2003; Rodriguez-Brenes and Peskin, 2010), the accumulation of defective mitochondria (Elson et al., 2001; Kowald et al., 2014; Kowald and Kirkwood, 2011; Tam et al., 2015), the breakdown of protein homeostasis (Proctor et al., 2005; Proctor et al., 2007; Proctor and Lorimer, 2011), and signalling pathways such as the Forkhead box protein O (FOXO) response (Smith and Shanley, 2010), the DNA damage response (Passos et al., 2010), stem cells (Glauche et al., 2011; Ro and Rannala, 2001; Taylor et al., 2003), and network models to explore the interactions between different mechanisms (Kowald and Kirkwood, 1996 and 2000; Sozou and Kirkwood, 2001). Many models have also been developed to specifically examine the processes involved in brain ageing and age-related neurodegenerative disorders (reviewed in Lloret-Villas et al., 2017).

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As well as modelling, systems biology involves the use of bioinformatic tools in order to try to understand how the many components involved in ageing interact (for example, genes, proteins). A recent review highlights some of the databases related to the ageing process (Tacutu et al., 2018). Vast amounts of high-throughput omics data are being generated, and this has led to new challenges in terms of data storage and analysis. Bayesian statistical techniques are being increasingly used to extract the maximum amount of information from data that are subject to errors and intrinsic noise (Wilkinson, 2007). Data storage and analysis require high computational power and need the use of parallel computer clusters or cloud computing. Software tools also need to be continually upgraded, and new tools developed, to keep pace with new technologies for data acquisition.

Conclusion

This chapter has given an overview of some of the biological aspects of human ageing, with a particular emphasis on damage to molecular and cellular components by ROS. The mechanisms involve many complex interactions, and as we have seen, vicious cycles of damage leading to more damage are a common theme. Our understanding of the processes involved in ageing are still far from complete, but the vast improvements in experimental techniques and computing power have greatly advanced our knowledge over recent years. However, this has brought new challenges with regard to making sense of the increasing amounts of data. It is also necessary to be able to integrate data and hypotheses in order to gain a better understanding of the ageing process.

Therefore, research into ageing now requires a multi-disciplinary team of bioinformaticians, statisticians, computer programmers, and mathematical modellers, in addition to clinicians and experimental scientists.

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The ageing brain

Chapter: The ageing brain

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Introduction

Cross-sectional and longitudinal studies have convincingly demonstrated evidence for a slowly progressive decline in cognitive abilities, including memory performance, processing speed, and flexibility with age (Alberts et al., 1997). Age-associated deficits in several other spheres, including motor dexterity, are also referable to declining function within the central nervous system (CNS). The aetiology of progressive age-related CNS dysfunction has remained elusive. Post-mortem studies have revealed that, in many cases, microscopic changes identical to those found in classical neurodegenerative disorders are present in the brains of aged individuals without dementia. For example, Alzheimer-type neurodegenerative changes in vulnerable brain regions are virtually universal in individuals aged 60 and over. In this context, a pathophysiological continuum bridging brain ageing with classical neurodegenerative disease seems axiomatic, wherein the functional deficits accompanying 'normal' brain ageing are simply consequent upon

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the development of disease-specific neurodegenerative pathology, occurring at a level below the threshold of full-blown clinical manifestation. However, this concept is problematic. It ignores the large body of evidence for neuronal (and glial) changes at the cellular and molecular levels that occur in the setting of brain ageing per se and that can be divorced from canonical disease-specific cellular pathologies (e.g. plaques and tangles). So understanding the mechanisms underlying pure brain ageing is predicated on elucidating the factors underlying the development of these 'quasi-pathological' age-associated changes. Moreover, there are important implications for understanding the relative mechanisms underlying ageing and AD. Specifically, these age-related changes may lower the threshold for canonical neurodegenerative pathologies to manifest morphologically and clinically. Although studies in non-human primates and other animals have contributed substantially to our understanding of the ageing brain, the following discussion will focus on human studies.

Morphological changes

Gross changes

Features commonly encountered on gross external inspection of the aged brain include thickening and opacification of the leptomeninges, prominence of the arachnoid granulations, atherosclerosis, and tortuosity of the arteries comprising the circle of Willis, as well as variable degrees of cortical atrophy. Internal examination of the cut surfaces of slices reveals varying degrees of white matter loss and ventricular dilatation. The age-associated decline in brain weight provides a quantifiable index of diminishing volume. Autopsy studies suggest a relatively stable weight in the fifties and sixties after which brain weight declines progressively. However, there are caveats inherent in these unselected cross-sectional studies in which the contributions of confounding factors (such as nutrition, for example) are not universally taken into consideration. Moreover, more recent studies of cortical thickness have indicated minimal changes in the absence of cognitive dysfunction (Mouton et al., 1998). Finally, there may be differential involvement of cortical layers. For example, non-human primate studies have revealed that atrophy in advanced age is relatively confined to layer I, possibly reflecting age-related simplification of the axons and dendrites projecting into this layer from deeper strata (Peters et al., 1998). In contrast to the controversy concerning gross cortical alterations, there is widespread consensus that white matter atrophy and pathology represent a common accompaniment of ageing and that much of this is related to arterial pathology with attendant white matter ischaemia (Smith et al., 2000).

Histological changes

Comparative microscopic studies have revealed changes in neuronal number and size, organellar alterations, and reorganization of synaptic elements, including modifications in the shape and number of synaptic

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terminals, dendrites, and dendritic spines. There are age-associated alterations in glial cells and blood vessel elements as well. Evaluating the extent and significance of these changes is complicated by the phenomenon of selective vulnerability whereby some regions are more severely affected than others.

Quantitative neuronal changes

It has been estimated that there are 8.6×10^{11} neurons and 10^{14} synapses in the human brain (Pakkenberg et al., 2003). There has been considerable controversy concerning whether, and to what extent, there is a significant depletion of neurons in the non-diseased ageing brain. Much of this controversy derives from technical discrepancies and lack of methodological standardization among studies. The application of contemporary unbiased stereological techniques, including, for example, use of the 'optical fractionator' (West et al., 1991) which minimizes double counting of neurons, has addressed some of these issues. For the cerebral cortex, the degree of age-associated neuronal loss is not commensurate with cortical atrophy, suggesting that depletion of neuropil elements play a significant role in the latter. A study of 94 autopsy brains by Pakkenberg and Gundersen (1997) indicated a lifetime loss of only 10% of cortical neurons. Other studies, for example of the temporal (Gomez-Isla et al., 1997; Terry et al., 1987), frontal (Terry et al., 1987), parietal (Terry et al., 1987), and entorhinal cortices (Gomez-Isla et al., 1996; Morys et al., 1994a), were unable to document any depletion of neurons. The ageing hippocampus exhibits only a subtle loss of neurons, contrasting with the massive depletion which characterizes Alzheimer's disease (Simic et al., 1997; West et al., 1994). Like the cerebral cortex and hippocampus, many of the subcortical structures that have been examined in the ageing human, including the medial mammillary nucleus (Begega et al., 1999), hypothalamus (Morys et al., 1994b), and nucleus basalis of Meynert (Chui et al., 1984), display negligible neuronal loss. Whether there is a significant loss of noradrenergic neurons from the locus coeruleus, a phenomenon which could have implications for age-related behavioural and emotional changes (including age-related depression), is a matter of controversy (Manaye et al., 1995; Mouton et al., 1994; Ohm et al., 1997).

One area of the brain in which there is general consensus regarding a significant age-associated loss of neurons is the substantia nigra pars compacta. This nucleus harbours the dopaminergic neurons that project to the basal ganglia and that degenerate in Parkinson's disease (PD). Estimates of nigral neuronal loss are in the order of 10% per decade (Ma et al., 1999). The selective vulnerability of this neuronal population is interesting in the context of the unique age-related cellular changes that it exhibits and that are distinct from those found in classical neurodegenerative diseases (see below).

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Loss of neuronal synapses, irrespective of cell body depletion, has been described in ageing and may represent a key substrate underlying the loss of 'cognitive reserve', a phenomenon that reduces the threshold for dementia in the setting of superimposed Alzheimer-type neurodegenerative changes. In a study of the frontal cortex from 25 individuals without dementia aged 16–98 years, Masliah et al. (1993) described a significant inverse correlation between presynaptic terminal density and age and a 20% loss using the age of 60 years as cut-off. Importantly, the authors concluded that this was independent of beta-amyloid deposition. Post-synaptic alterations in ageing, which seem to correlate with the degree of functional impairment, have also been described, including decreased spine density (Anderson and Rutledge, 1996). Age-related changes in spine morphology and volume (Kasai et al., 2010) have also been described. Notably, some studies in lower animals have documented age-related increases in synaptic density at both the presynaptic (Benice et al., 2006) and post-synaptic (Connor et al., 1980) level.

Finally, glial cell changes are common in ageing. Increased proliferation of astrocytes and increased expression of their constituent intermediate filament protein GFAP have been demonstrated in the human brain (David et al., 1997; Hansen et al., 1987). Studies have also indicated evidence for progressive microglial activation in the ageing primate brain (Sheffield and Berman, 1998; Sloane et al., 1999).

Cellular inclusions in brain ageing

Ageing neurons and glial cells are characterized by the accumulation of substances within their cytoplasm and sometimes their nuclei. It is generally acknowledged that this reflects age-associated dysfunction of the catabolic mechanisms which normally eliminate these substances, culminating in the formation of microscopically visible 'inclusion bodies'. These can comprise lipid or proteolipid components, complex carbohydrates, or proteins. The latter are analogous to the inclusions that define classical neurodegenerative disorders, and their formation invites speculation regarding the mechanistic overlap between brain ageing and pathological neurodegeneration.

Lipofuscin and corpora amylacea

Lipofuscin, also known as 'ageing pigment', is a membrane-bound complex mixture of oxidized protein and lipid degradation residues, along with lesser amounts of carbohydrates and metals. It accumulates in post-mitotic cells such as neurons (Fig. 2.1A). The topographic pattern of distribution of lipofuscin accumulation displays a particular predilection for certain areas. It is prominent in areas of the brain and spinal cord involved in initiating, monitoring, and controlling movement, including the inferior olivary nucleus (Fig. 2.1A), the dentate nucleus of the cerebellum, the globus pallidus, and the motor neurons in the anterior horn of the spinal cord and brainstem (Gray and Woulfe, 2005).

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Lipofuscin abundance increases with age in the cerebral cortex as well. Like some of the age-associated inclusion bodies discussed below, accumulating evidence suggests that lipofuscin is not benign but can impair cellular functions, including the ubiquitin-proteasome system.

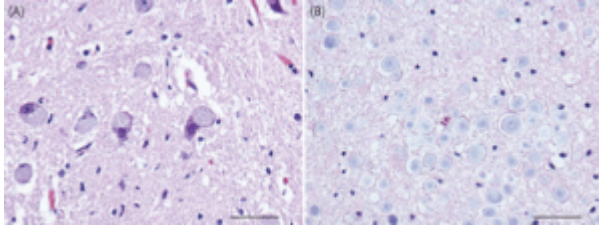


Fig. 2.1

Distribution of lipofuscin and corpora amylacea. A) Neurons in the inferior olivary nucleus show distention of their cell bodies by intracytoplasmic accumulation of lipofuscin. B) Corpora amylacea in layer I of the entorhinal cortex. Both sections stained with hematoxylin and eosin.

Bars=50µm.

Corpora amylacea (Fig. **2.1B**) are spherical, laminated structures composed of complex carbohydrate and localized within the distal processes of astrocytes in the brain of elderly individuals (Mrak et al., 1997). They are most frequently localized at the surface of the brain and around blood vessels. They are particularly abundant in a disease known as adult polyglucosan body disease, but whether they have any pathological significance in the non-diseased ageing brain is unknown.

Proteinopathy in brain ageing

Neurodegenerative diseases are characterized pathologically by the abnormal accumulation of proteins in neurons and/or glial cells. These protein aggregates form microscopically visible ‘inclusion bodies’, the morphology, distribution, and biochemical composition of which inform neuropathological diagnosis. A blurring of the interface between neurodegeneration and ‘normal’ brain ageing owes much to the identification in the brain of clinically non-diseased aged individuals of changes that define classical neurodegenerative diseases. Extracellular plaques (Fig. **2.2A**) and intraneuronal tangles (Fig. **2.2B**) comprising beta-amyloid and tau protein, respectively, are the histopathological hallmarks of Alzheimer’s disease (AD). These lesions predate the manifestation of cognitive symptoms by several years. Consequently, they are also commonly encountered on post-mortem examination of the brain of non-demented (presumably pre-symptomatic) elderly individuals. Modern imaging studies, most notably positron emission tomography (PET) imaging using beta-amyloid tracers such as Pittsburgh compound B, have confirmed the presence of significant beta-amyloid deposition

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within the brain of a large proportion of non-demented elderly individuals (Fjell et al., 2013; Gordon et al., 2016). Such studies, combined with magnetic resonance imaging (MRI) assessments of cerebral atrophy (regarded as a proxy measure of neurodegeneration), have been used to develop a clinical classification scheme for assigning individuals into one of four categories—those with beta amyloidosis (A) and neurodegeneration (N) are designated A+N+ and represent patients with AD; A-N- and A-N+ subjects represent non-diseased individuals and those with suspected non-AD pathology ('SNAP'), respectively (Gordon et al., 2016). In general, the A+N- group is thought to consist of subjects with preclinical AD, suggesting that this classification scheme advocates the concept of a pathological continuum of beta-amyloid deposition, beginning in the pre-symptomatic stages of the disease.

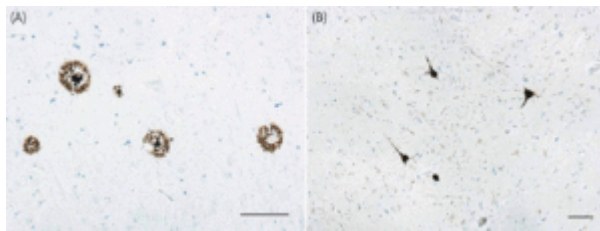


Fig. 2.2

Histopathological hallmarks of Alzheimer's disease. A) Extracellular plaques in the frontal cortex of a non-demented elderly individual revealed by immunohistochemical staining for beta-amyloid protein. B) Intraneuronal neurofibrillary tangles in the entorhinal cortex of a non-demented elderly individual revealed by immunohistochemical staining for tau protein.

Bars=100µm.

However, there is also evidence that Alzheimer-type neurodegenerative changes can develop in the setting of brain ageing per se and do not necessarily portend progression to AD or even dementia. For example, it appears that not all A+N- individuals progress to clinical AD. Also, neuronal tau pathology has been described in the brain of non-demented elderly individuals. Specifically, 90% of non-demented subjects under 30 years of age show pathological tau deposition in certain brain areas, most notably the noradrenaline-producing locus caeruleus in the brainstem (Braak et al., 2011). More widespread neuronal tau deposition is frequent in advanced age. The term 'primary age-related tauopathy' or 'PART' has been proposed for those individuals with tau-immunoreactive neuronal tangles but lacking beta-amyloid deposition (Crary et al., 2014). This is thought to be a correlate of the clinically assessed SNAP. Moreover, astrocytic tau pathology in the form of a recently described entity known as age-related tau astrogliopathy ('ARTAG') has been identified as a very common accompaniment of non-pathological brain ageing predominantly, though not exclusively, in individuals over 60 years of age (Kovacs et al.,

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2016). Thus, like the phenomena discussed below, PART and ARTAG represent neurodegenerative changes that could conceivably contribute to the development of the progressive cognitive and motor deficits that are commonly accepted as being within normal limits among aged subjects.

Mention should also be made of transactive response DNA-binding protein 43 (TDP-43). Accumulation of this neuronal RNA-binding protein to form intraneuronal cytoplasmic, and sometimes nuclear, inclusion bodies is the defining histopathological hallmark of amyotrophic lateral sclerosis (ALS) and some forms of frontotemporal dementia (Neumann et al., 2006). However, it has also been described in a significant proportion of brains with Alzheimer's disease and dementia with Lewy bodies, as well as in up to 18% of neurologically intact controls (McAleese et al., 2017), suggesting an independent role in age-related neurodegeneration. The TDP-43 protein has domains that are intrinsically disordered (lacking any stable three-dimensional structure), a recurrent theme in RNA-binding proteins. FUS (fused in sarcoma) is a second example of a highly disordered RNA-binding protein that has been associated with ALS (Daigle et al., 2013). This family of intrinsically disordered proteins seems particularly prone to aggregation upon accumulation and/or post-translational modification, and the particular vulnerability of neurons to dysregulation of this family of proteins may relate to their recurring roles as critical hubs of scale-free regulatory networks (reviewed in Gray and Woulfe, 2013). Although they are still in their infancy, studies of the role of RNA-binding protein aggregation in cellular ageing are producing provocative results (Lechler and David, 2017).

Unlike the examples discussed above, the protein composition of several inclusion bodies encountered in the aged brain remains unknown. These can be identified microscopically on the basis of their tinctorial properties using conventional histological stains and/or their immunostaining for ubiquitin. Ubiquitin is a small protein which binds to cellular proteins destined for proteasomal degradation. Because inclusion body proteins are ubiquitinated, their localization using immunohistochemistry can be exploited to visualize neuronal and glial inclusions whose principle protein constituent is as yet unknown. A variety of ubiquitinated inclusion bodies have been described in specific regions of the brain of non-diseased aged individuals (Dickson et al., 1990; Gray et al., 2003). These are generally perceived as benign, non-pathological entities. However, by analogy with their morphological similarity to disease-associated inclusions, it is tempting to ascribe a role to them in age-associated neurological dysfunction (Gray et al., 2003). Marinesco bodies are instructive in this regard. These are ubiquitinated spherical intranuclear inclusion bodies which accumulate with age in substantia nigra dopamine neurons in the non-diseased human substantia nigra (Fig. 2.3A) (Dickson et al., 1990). They were traditionally considered to be benign, non-pathological entities. However, more recent studies indicate that their formation may contribute to the motor deficits that accompany 'normal'

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ageing (Abbott et al., 2017; Beach et al., 2004; Kanaan et al., 2007). In this context, Marinesco bodies could reasonably be considered 'quasi-pathological' entities. Similar (although less intensively studied) ubiquitin-positive inclusions in the normal ageing brain include granular cytoplasmic inclusions in neurons of the inferior olivary nucleus (Fig. 2.3B) (Dickson et al., 1990), spider web-like cytoplasmic inclusions in large (presumably cholinergic) neurons in the neostriatum (Fig. 2.3C) (Kawashima et al., 2000; Oyanagi et al., 1994), and 'colloid' or 'hyaline' inclusions often found in hypoglossal and spinal motor neurons in the elderly (Mendell and Markesbery, 1971). Ubiquitin-positive axonal swellings are seen with increasing age in certain parts of the CNS (Dickson et al., 1990), most predominantly in the cuneate and gracile nuclei, which are targets of sensory information arising in the arms and legs, respectively. Ubiquitin-immunopositive granular bodies and dot-like structures are also commonly encountered in the ageing brain (Dickson et al., 1990, 1992). The granular bodies are believed to be located in the distal aspects of dystrophic neurites. They are most commonly encountered in the middle and upper cortical layers, especially layer II of the entorhinal cortex. This is potentially important, because these neurons form a crucial link in the circuit responsible for short-term memory. Ubiquitin-positive dot-like structures can be prominent in the ageing white matter and appear to be located in oligodendroglia and myelin lamellae (Dickson et al., 1990). Finally, there are age-associated cytoplasmic inclusion bodies of unknown protein composition that do not stain for ubiquitin, including eosinophilic cytoplasmic inclusions in neurons of the thalamus (involved in relaying sensory information), substantia nigra (involved in motor control) (Pena, 1980; Pena and Katoh, 1989), and the external cuneate nucleus (involved in relaying information from the upper limbs) (Fig. 2.3D) (Ito et al., 2016), as well as neuronal intranuclear rodlets (Woulfe and Munoz, 2000). The extent to which these cellular changes contribute to progressive age-related deficits referable to the various nuclei remains to be explored. Proteomic studies of these structures could be informative in this regard.

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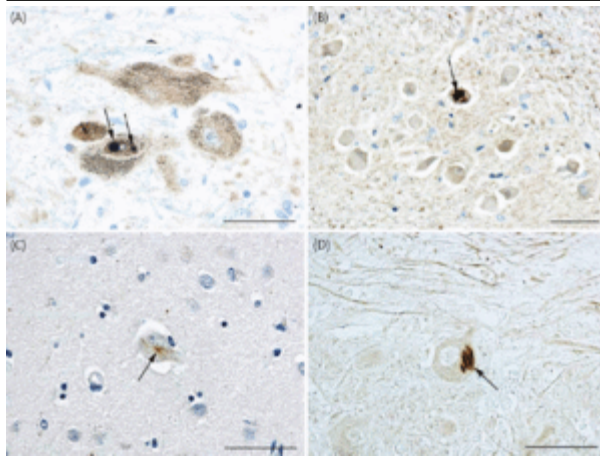


Fig. 2.3

Proteinaceous intraneuronal inclusion bodies found in non-diseased brains. A) Marinesco bodies (arrows) in the nucleus of a pigmented neuron in the substantia nigra. B) Granular inclusions (arrow) in the cytoplasm of an inferior olivary neuron. C) Spider-web-like inclusion (arrow) in the cytoplasm of a large interneuron in the striatum. D) Complex linear inclusion (arrow) in the cytoplasm of a neuron in the external cuneate nucleus. A–C stained for ubiquitin. D stained for class III beta tubulin.

Bars=50μm.

Degenerative changes in the enteric system and potential propagation of pathology to the central nervous system

The focus of this chapter has been the plethora of age-related changes within the CNS, but the enteric nervous system (ENS) is not exempt from age-related deterioration, and the possibility exists for prion-like transmission of molecular agents of pathology between these nervous systems (as will be elaborated later). The human ENS comprises 400–600 million neurons, a sizeable population roughly comparable to the neuronal content of the spinal cord (Furness, 2012). These neurons coordinate motility through the gastrointestinal (GI) tract, as well as secretion and absorption. It is reasonable to assume that the GI complaints (dysphagia, reflux, constipation, and incontinence) that are prevalent in the elderly to some extent arise from age-related dysfunction of the ENS, though the data are surprisingly inadequate for detailed specification of the affected neurons and their loss of function over time. At a gross level, a 40% increase in transit time through the human GI tract has been documented in older subjects, compared to a younger cohort (Madsen and Graff, 2004). This figure is in close agreement with a mouse model in which functional inactivation of UCHL1 results in precocious loss of function of ENS neurons (Coulombe et al., 2014). Unlike the CNS, which exists in the stable and privileged environment

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conferred by the blood-brain barrier, the ENS is situated in close proximity to a highly variable stream of ingested substances and microbes, some of which can be acutely toxic or have cumulative pathogenicity. The homeostatic mechanisms that promote a uniform environment in the CNS, with respect to oxygen tension, glucose levels, reactive oxygen, and so forth, could not prevail in the gut, which contains a topologically exterior environment hosting microbes with their own metabolic agenda. In healthy individuals, the microbiome (a collection of prokaryotes, eukaryotes, and viruses) exists in a mutually beneficial (commensal) relationship, providing catabolic services that are beyond the capacity of the host, in return for a supply of complex macromolecules and a thermally regulated environment. Given the proximity of the ENS to the microbiota of the gut, it would not be surprising if dysbiosis (a detrimental alteration in the constituents of the microbiome) affected ENS function, and dysbiosis is common in GI diseases such as Crohn's disease, irritable bowel syndrome, and coeliac disease (Clemente et al., 2012). The diversity of the microbiome may decrease with age and is reduced upon feeding of institutional meals in long-term care facilities (Claesson et al., 2012). Dysbiosis may have deleterious effects on the ENS, which could increase transit times in a feed-forward loop of enteric dysfunction.

An intermittently hostile environment and exposure of ENS neurons to passing toxins and pathogens can be expected to wreak havoc on cellular constituents. As previously described (above and in Chapter 1), proteins are sensitive to misfolding and subsequent aggregation as a consequence of environmental insults. If, upon misfolding, such proteins can template the misfolding of additional protein molecules of the same type, there is the possibility of an accumulation of the misfolded entity with time. If a misfolded protein with this templating property can escape the cell and enter an adjacent or distal cell, there is the further possibility of prion-like transmission. There has been a proliferation of publications in the recent literature supporting such a mechanism in prominent age-related neurodegenerative conditions, including AD and PD (reviewed in Goedert et al., 2017). In the case of PD, oligomeric aggregates of α -synuclein have been postulated to act as the prion-like entity. α -synuclein is particularly abundant in the vermiform appendix (Gray et al., 2014) where inflammatory episodes and close proximity to gut contents could initiate aggregation within enteric neurons. The vagus nerve would provide a conduit for prion-like spread of aggregated α -synuclein from the appendix or other enteric sites to the brain, and in accordance with this model, truncal vagotomy has been found to reduce the incidence of PD (Svensson et al., 2015). Various mechanisms have been proposed for the transmission of prion-like proteins from one neuron to the next, including direct transmission through tunnelling nanotubes or indirect transmission through secreted exosomes. Validation of such mechanisms *in vivo* is an area of current research.

Neuroinflammation

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Microglia

Microglia are resident innate immune cells and comprise about 16% of the human brain. The distribution of these cells throughout the brain is not uniform, with higher density in the white matter. Microglia are normally in a resting state, taking on a ramified appearance with long, thin processes extending from the cell body, with which they survey the surrounding environment. In the normal healthy brain, on detection of any abnormalities, microglia become activated (primed) and respond to restore homeostasis, e.g. by phagocytosis of cellular debris. Although microglia are neuroprotective under non-pathological conditions, overactivation of microglia leads to an increase in oxidative stress and inflammation.

It has been shown that there is increased priming of microglia in the ageing brain (reviewed in Norden and Godbout, 2013) and in age-related neuropathological conditions, e.g. in AD (Hoeijmakers et al., 2016). This may be due to an increase in pro-inflammatory stimuli such as lipopolysaccharide (LPS), protein aggregates, and neuronal damage. The chronic activation of microglia is accompanied by the release of pro-inflammatory cytokines, reactive oxygen species (ROS), and nitric oxide, and also the up-regulation of surface receptors, e.g. complement receptors and major histocompatibility complex (MHC) (Norden and Godbout, 2013).

There is evidence of overactivation of microglia in both PD (reviewed in Block and Horn, 2007; Long-Smith et al., 2009) and AD (reviewed in Mandrekar and Landreth, 2010; Solito and Sastre, 2012). The first evidence of this was shown by an increase in the MHC class II cell surface receptor HLA-DR in the substantia nigra of post-mortem brain of both AD and PD patients (McGeer et al., 1988). Since then, many inflammatory markers have been found in human PD post-mortem brains, e.g. tumour necrosis factor (TNF)- α , interleukin (IL)-1 β , and IL-6 (reviewed in Lull and Block, 2010). In particular, dopaminergic neurons (found in the substantia nigra) are damaged by cytokines and loss of these neurons is associated with PD. It has been shown that LPS is only toxic to dopaminergic neurons in the presence of activated microglia which release pro-inflammatory mediators, e.g. NADPH (Qin et al., 2004). It is not yet known why dopaminergic neurons are more susceptible to damage via microglial activation, but it has been speculated that they may be more vulnerable to oxidative stress (Block and Horn, 2007). Notably, recent studies have demonstrated that these neurons are capable of expressing MHC class I protein (Cebrián et al., 2014). These neuroinflammatory factors may account (at least in part) for the susceptibility of substantia nigra neurons to age-related degeneration, as discussed earlier. In AD, it has been shown that microglia are only associated with dense plaques, not diffuse plaques, suggesting that they do not initiate aggregate formation (Itagaki et al., 1989). Amyloid plaques are normally cleared by microglia, but on the other hand, microglia may cluster around plaques and become activated (Sasaki et al., 1997). In

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particular, macrophage scavenger receptor (MSR) A-positive microglial cells have been shown to form these clusters and a positive association between pathological amyloid and the number of MSR A-positive clusters has been found (Zotova et al., 2013).

An interesting study into the role of microglia in dementia with AD pathology was carried out on 299 post-mortem brains donated by participants of the MRC-Cognitive Function and Ageing Studies (CFAS) (Minett et al., 2016). Using immunohistochemistry, they examined five markers of microglial function: Iba1 (microglial motility); CD68 (phagocytic activity); HLA-DR (immune response and a genetic risk factor for AD); MSR A (clustering of microglia around plaques); and CD64 (systemic immunity). They found that high levels of CD68, MSR A, and CD64, and low levels of Iba1 were significantly associated with dementia.

Some immunotherapy approaches use antibodies that facilitate the clearance of amyloid plaques via microglia, and it has been suggested that this is mediated via Fcγ receptors and autophagy (reviewed in Valera et al., 2016).

Complement

The complement system is part of the innate immune system and can be activated by three different biochemical pathways: classical complement; alternative complement; and lectin pathway. Each pathway is activated by different factors but, in each case, leads to the formation of the membrane attack complex (MAC). Over 30 factors (C factors) make up the system, many of which have been shown to be upregulated with ageing (Cribbs et al., 2012). It has been suggested that this may be a protective response to an increase in cellular debris with age. However, chronic activation of complement could be harmful as the MAC can damage cell membranes. Immunohistochemical studies in the 1980s showed that C factors are associated with amyloid (reviewed in Veerhuis et al., 2011). There is also direct evidence that plaques activate complement *in vitro* (Rogers et al., 2012), and indirect evidence that this occurs *in vivo* (Rogers et al., 2012). C factors are expressed at different Braak stages. For example, C1q, C4d, and C3d are found in plaques at early stages, but at later stages, these factors are increased in plaques and also appear in tangles. On the other hand, C5b-9 is only found at late stages in plaques and tangles (Veerhuis et al., 2011). However, fewer complement genes change their expression in AD, compared to non-pathological ageing (Cribbs et al., 2012). A GWAS study identified that, like APOEε4, polymorphisms in the clusterin (*CLU*) and C3b/C4b receptor 1 (*CR1*) genes are risk factors for AD (Lambert et al., 2004). A follow-up study showed that the CR1-S isoform is associated with an increased risk of AD and has more binding sites that increase co-factor activity to inhibit complement activation; however, further functional studies are required (Brouwers et al., 2012). In summary, the evidence suggests an increase in complement activation in normal brain ageing as a compensatory mechanism. On the other hand, either chronic activation or down-

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regulation of complement pathways is detrimental and contributes to pathology in the ageing brain.

Variability in brain ageing

Genetic risk factors

Many genetic risk factors that contribute to brain ageing and neurodegeneration have been identified and contribute to the inter-individual variability that characterizes age-associated cognitive decline. Mutations in particular genes, e.g. *APP* and *UCH-L1*, increase the risk of familial early-onset diseases, whereas polymorphisms, e.g. *APOE*, increase the risk of late-onset disease. GWAS have identified many gene variants associated with neurodegeneration at a genome-wide significance level, suggesting that these disorders are polygenic. This means that an individual's susceptibility to disease depends on a large combination of genetic factors contributing to a wide variation in the actual underlying molecular mechanisms that initiate the disease process.

One study used an integrative genomics approach, called differential ageing, to quantify the ageing rate in the human cerebral cortex (Rhinn and Abeliovich, 2017). They followed this up with a genome-wide scan and identified *TMEM106B* and *progranulin* (*GRN*) variants that interact in the same pathway and are associated with inflammation, neuronal loss, and cognitive deficits in older individuals (over 65 years) without known neuropathology. Individuals with these variants had a higher rate of biological ageing. Interestingly, both of these proteins are involved in microglial function.

Epigenetics

Epigenetic factors, such as methylation, acetylation, and non-coding RNAs, regulate gene transcription and have an important role in brain ageing. As epigenetic mechanisms are reversible and linked to lifestyle factors, such as diet and physical activity, there has been a lot of interest in their potential as therapeutic targets to ameliorate cognitive decline (Delgado-Morales et al., 2017). In the following discussion, we give some specific examples, but this is by no means exhaustive and is a rapidly expanding field of research.

The process of DNA methylation results in the covalent addition of methyl groups to DNA molecules at cytosine residues, especially at CpG dinucleotides. If methylation occurs in the promoter region of a gene, transcription is repressed. However, the human genome contains CpG-rich sequences, known as CpG islands, which are normally unmethylated. These regions are usually found in gene promoters or within gene bodies and regulate transcription. During ageing, there is a global decline of DNA methylation, but in specific genomic regions, there is an increase in both hypermethylation (in CpG islands) and hypomethylation events (in repetitive tandem and interspersed elements), which are termed age-differentially methylated regions (a-DMRs). These events occur due to

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environmental or stochastic factors. This leads to an increase in DNA methylation variability at certain CpG sites, a phenomenon known as epigenetic drift with age. Interestingly, at older ages (75+), epigenetic convergence has been observed in the human brain (Oh et al., 2016).

Epigenome-wide association studies (EWAS) on ageing have been used to identify an epigenetic clock by examining tissue-specific a-DMRs (Bacalini et al., 2017). In addition, there have been many studies comparing the DNA methylation age (DNAmAge), as determined by the epigenetic clock and the chronological age of an individual. This has shown that the estimated DNAmAge tends to be higher than the actual chronological age in several age-related conditions, including AD, PD, and Down's syndrome (reviewed in Bacalini et al., 2017).

Age-associated alterations in gene expression have also been described at the post-transcriptional level. As discussed earlier, there are changes in the solubility, localization, and activity of RNA-binding proteins which may underlie age-related alterations in the stability and splicing of RNAs. In addition, non-coding RNAs are RNA molecules that are not translated into protein and include microRNAs (miRNAs), small nucleolar RNAs (snoRNAs), small interfering RNAs (siRNAs), and long non-coding RNAs (lncRNAs), all of which are involved in regulating mRNA transcription and translation. The most extensively studied of these, miRNAs, are short RNA molecules (~22 nucleotides) and function to silence gene expression by either enhancing mRNA degradation or inhibiting translation. Each miRNA targets a specific set of genes and each gene may be regulated by several different miRNAs, providing a complex network of gene regulation. The effect of miRNAs in gene regulatory circuits has been extensively studied with the aid of mathematical modelling and includes fine-tuning of gene expression, prevention of leaky gene transcription, generation of pulse-like responses, and induction of switch-like behaviour (Lai et al., 2016). Many miRNAs are tissue-specific, and several are highly enriched in brain, such as miR-124 that downregulates polypyrimidine track binding protein 1 (*PTBP1*), a repressor of neuronal differentiation (Makeyev et al., 2007).

The involvement of miRNAs in neurodegeneration may be either direct via repression of genes such as *APP* (Hébert et al., 2009), *BACE1* (Hébert et al., 2008a), or α -synuclein (Doxakis, 2010) or indirect via repressing genes important in maintaining protein homeostasis (Sin and Nollen, 2015). In AD patients, several miRNAs have been shown to be consistently dysregulated (reviewed in Femminella et al., 2015), including miR-9, miR-34, miR-107, and miR-29.

miR-9 is highly expressed in the developing and adult brain and has an important role in promoting neural differentiation (Coolen et al., 2013). Many studies have shown it to be decreased in AD, and it has been demonstrated to be down-regulated by A β (reviewed in Van den Hove et al., 2014). The targets of miR-9 include FGFR1, NF κ B, SIRT1, and REST. SIRT1 is important in the brain due to its role in energy metabolism, the

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circadian rhythm, stress response, and cell survival pathways (reviewed in Ng et al., 2015).

miR-34 regulates the expression of the transcription factor p53. In AD patients, miR-34 is present at high levels in the hippocampus and leads to increased expression of p53 (by targeting a p53 inhibitor, e.g. HDM4). p53 indirectly induces tau phosphorylation (Hooper et al., 2007) and also induces the expression of miR-34, so that there is a positive feedback loop between miR-34 and p53. So the increased levels of miR-34 in AD may contribute to hyper-phosphorylation and aggregation of tau.

miR-107 is normally abundant in the temporal cortex but is decreased in the early stages of AD (Wang et al., 2008). The same group later found a correlation between decreased miR-107 and levels of neuritic plaques and tau tangles (Nelson and Wang, 2010). BACE-1, an endopeptidase that cleaves amyloid- β precursor protein (APP) to produce neurotoxic amyloid peptides, is a target of miR-107 and it has been speculated that the decrease in miR-107 contributes to disease pathology through increased levels of BACE1 (Wang et al., 2008).

miR-29 is significantly down-regulated in AD and targets beta-site amyloid precursor protein-cleaving enzyme 1 (BACE1) at the protein level, not the mRNA level (Hébert et al., 2008b). In this study, Hébert et al. found that in a subgroup of AD patients with high BACE1 levels, miR-29a, and miR-29b-1 are significantly reduced.

Environmental/lifestyle factors

It is well known that there are interactions between genetics, epigenetics, and environmental/lifestyle factors (Jaenisch and Bird, 2003). In particular, there is evidence to suggest that the ageing brain retains functional plasticity and can be affected by lifestyle factors such as diet and physical activity (Fig. 2.4). It has been shown that physical activity may slow down the progression of neurodegeneration (e.g. Rolland et al., 2008). In addition, physical activity can modify genetic risk factors such as APOE ϵ 4 in a mouse model (Nichol et al., 2009). As well as physical activity, cognitive activity and social interactions have been shown to slow down ageing of the brain (e.g. de Frias et al., 2014).

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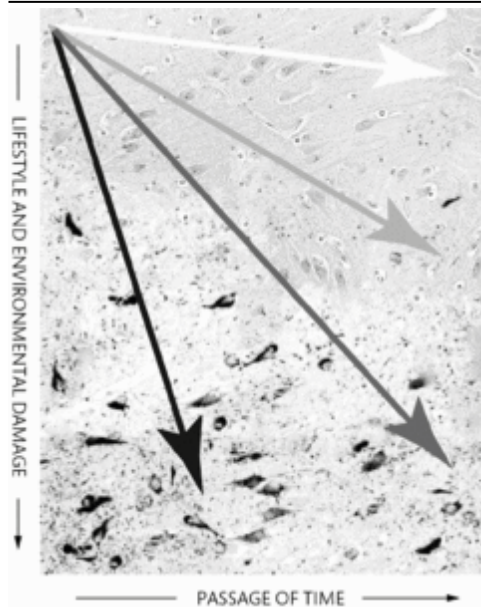


Fig. 2.4

Lifestyle and environmental factors lead to a gradient of pathology (as shown with the arrows) with age. The figure is a digitally generated composite of histological sections from healthy and diseased brains.

Studies in animals have clearly shown that environmental enrichment potentiates learning and memory and show increased expression of neurotrophic factors in several areas of the brain (reviewed in Mora, 2013). The experimental data demonstrate the plasticity of the brain and explain the benefits of cognitive and physical activity in older persons to prevent or delay the onset of dementia. Confirmation of findings in model systems could come from population-based studies in humans. Towards this end, variability in brain ageing is currently being analysed in a German cohort (Caspers et al., 2014). The aim of this study is to investigate the influence of genetic, environment, and health status on structural and functional variability in the ageing brain.

Conclusion

By the simple metric of oxygen consumption, it is clear that the brain displays a very high level of metabolic activity relative to other tissues, but despite the molecular damage that this activity necessarily entails (and the very limited and spatially restricted replacement of constituent neurons), the brain can execute its functions for more than a century. Careful analysis of aged brain tissue from 'healthy' centenarians (those not diagnosed with neurodegenerative diseases) reveals perturbations in cell numbers and cell morphology generally associated with pathologic states, so it would appear that with the passage of time, there is no escape from molecular mayhem. The proper functioning of neurons and associated cells relies on intact layers of molecular machinery from the

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genome (and its complex epigenetic regulation) to RNA (with its increasingly baroque processing and homeostasis) to proteins (and all manner of post-translational modifications and their consequences). There is much here that can go wrong. Given enough time, it invariably will, but much remains to be learnt about which perturbations are most critical for brain ageing and what effective interventions can be contemplated.

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The sociology of ageing

Chapter: The sociology of ageing

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Ageing as a social process

The sociology of ageing explores the social circumstances and choices that shape, support, or distort life-course developments, from large-scale social structures through to the micro-interactions that make up people's experiences of their own ageing and the cultural practices generating shared expectations about what ageing involves. The field itself has evolved over time, as it tries to come to terms with the complexity of these phenomena and the ways in which they affect each other.

Social environments and relationships impinge on ageing in all its aspects, both positively and negatively. They also, in part, *constitute* it. Physical, conceptual, and experiential aspects of ageing depend in different ways on the social settings in which they occur. Healthy ageing is associated with status and relative power; the higher someone is in a social structure, the more likely that person is to live longer (Donkin et al., 2002; Woolf et al., 2015), as well as to feel that ageing makes it

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possible to fulfil personal goals (McGee et al., 2011). Much of this applies too between societies and over time. Standard life-courses in the West—and in large part elsewhere—contrast with those before the Industrial Revolution, partly because modern societies involve new living conditions, not least practices relating to nutrition, hygiene, and housing. ‘Viewed in the early 1950s as shaped almost entirely by biological processes and medical care, physical health and illness are now understood to be as much or more a function of social, psychological, and behavioural factors’ (House, 2001: p. 125; Marmot et al., 2012). But social resources, attitudes, and habits also affect what it means to be an (older) person. If older people are envisaged as feeble and incompetent, even publicly described as such (Fealy et al., 2012), these expectations will constrain their activities; they may ‘auto-stereotype’ themselves (Stuckelberger et al., 2012). Social ideas about ageing impact decisively on older people, opening or closing possibilities open to them (Bytheway, 2011). But the fact that societies themselves constantly change makes ageing a variable process, in which life-courses are enacted in contrasting ways. There is no neutral baseline for ‘normal’ ageing, since forms of senescence are so heavily affected by social settings.

The social circumstances of late industrial societies are certainly historically untypical as far as human lifetimes are concerned. Ironically, this has not led to broader public awareness of the ways ageing is socially constructed. Ageing is often portrayed simply in terms of risk and danger, depicted as generating an alarming social burden. Purportedly objective calculations buttress this vision. In reality, social and political choices mould the shapes that ageing takes and whether it presents problems or opportunities. On the one hand, ‘population ageing’ is described without context as threatening in itself; on the other, modern science may be envisaged as a source of potentially ageless vitality, the mythological ‘fountain of youth’. These debates themselves are social phenomena, attesting to contrasting conceptions of ageing in different arenas.

Examining human ageing in different cultural and temporal contexts illuminates recent changes. By the 2030s, the shape of the human population ‘pyramid’ will have taken just over a century to shift from the broad-based triangle typical of most mammals to an approximate rectangle, with roughly equal numbers of individuals at each life-stage (Treas, 1995). Yet this does not mean that older adults in past societies were necessarily rare—the most drastic changes in survival rates have affected children under 5. In the early sixteenth century, an English aristocrat who had survived to be 21 could expect to live to 72—‘three score years and ten’ (Lancaster, 1990). A profound, but often ignored, impact of population ‘rectangularization’ is its dissociation of *death from birth*. In the past, death was a constant threat in childbirth or childhood; mothers and children who survived still had to contend with the deaths of other infants or siblings. Now, death is envisaged as happening at the opposite end of life from birth. This is a massive shift in social perception

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—death is no longer perceived as an ever-looming possibility, but as something that happens when one is *old*.

Older people often now receive considerable support, in that welfare states offer them degrees of protection never previously known; on the other hand, in western societies, ageing is often seen as a uniform mass process, which should not be allowed to become over-expensive. To counteract this homogenization, the 'life-course' approach to the sociology of ageing explores interactions between work, health, family membership, and other entwined experiences of individuals and groups over time. It highlights both the variability of these pathways and their connections to the social and political contexts that determine what should be expected from, and supported in, later life. For instance, taxation policy on pension funds is a matter of political decision, yet the decline of occupational pensions is often presented as inevitable (Macnicol, 2015), with impacts on employees' anxiety at all stages of their life-courses.

Popular debate ignores, too, the fact that modern societies could not contain relatively large proportions of older people without an equally striking global development—dramatic decreases in the readiness to have children (Samir and Lutz, 2017). If the UK birth rate returned to the level of the third quarter of the twentieth century, 'the population' might no longer count as 'ageing', whether longevity rates increased or not (Bytheway, 2011: p. 163ff). But social views on the desirability or otherwise of having children fluctuate. In the 1930s, fears about European population decline bolstered official support for family growth in some countries. Now, public discourses supporting the choice to remain 'child-free' compete with exhortations about the 'social responsibility' to have children (Institut für Demoskopie Allensbach, 2003). Individuals' views of their own life-courses, both prospectively in terms of the choices they make and retrospectively when they look back on them, also change. Older women who have raised families may look back on lives without careers and conclude they have 'done nothing' (Edmondson, 2015). Social changes, including ambiguous social attitudes to childbearing, can make it harder for individuals to interpret their own life-courses, and this applies at the level of whole societies too.

Since infant, child, and maternal mortality rates are now so low in the West, they offer little room for dramatic improvement; leaps in population-wide life expectancy seem unlikely to occur here in future (Dong et al., 2016). Increased life expectancy among adults has changed significantly, but more slowly. In Ireland, for example, where social change was relatively limited between the 1920s and the 1980s, especially for older generations, there was little change in the age at death of older men at all (Fahey et al., 2007: p. 12, Fig. 4). Adult life expectancy rates needed appropriate circumstances and policies if they were to improve.

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Life-course analyses accentuate awareness that much that happens to individuals in later life, as well as how they regard their own lifetimes, follows from what they have done, or what has happened to them, at earlier stages. These impacts range in scale from the effects of war or peace to educational arrangements in the past, and from health-related conditions in places of former work to expectations about family life. To be a single, middle-class woman, '29 and unmarried', 'a failure' without children—as Virginia Woolf put it in 1911 (Woolf, 1975: p. 466)—was to be engaged on a different life-course trajectory from that of a single woman of similar age a century later.

The social conditions of children and adolescents in a given society are related to the way adulthood and old age is perceived in that society; and, conversely, the role and position of adults and older people is affected by the treatment and roles of those in earlier stages of life.

(Hareven, 1982: p. 3)

Ageing, therefore, must be understood in context (Cole et al., 1992). 'Against the backdrop of history, changes in people's lives influence and are influenced by changes in social structures and institutions'; these, in turn, are 'linked to the meanings of age, which vary over time' (Riley et al., 1999: p. 327). In other words, views of what it means to be old change all the time (Featherstone and Hepworth, 1995), heavily affected by social and political developments.

Having a life-course itself is changing, affected by shifting global and local economies and patterns of work, family, and community relations, as well as religious and other sources of meaning. Yet older people are often constrained by stigmatizing expectations, attributed *because* of their age (Kunow, 2010)—'ageism'. The stereotypical perception and treatment of older people may actually have hardened during the twentieth century (Hareven, 1982; Katz, 1996), affected by states' bureaucratic practices and their impacts on the 'social imaginaries' of entire societies (Gaonkar, 2002)—how they perceive ageing. Age became treated as a 'master trait', a feature dominating perception of the person who has it. It is hard to disguise, signalling a chronological trajectory against which individuals' achievements and qualifications can be measured. A whole concatenation of official documents, birthdays, and time-related social expectations make age seem crucially important (Bytheway, 2011). Yet this trope in social judgment grossly oversimplifies the 'multidimensional' ways in which life-courses are actually lived out, 'structured by virtue of the order and timing of multiple social roles over the life span' (Macmillan, 2005: p. 6).

'Ageing' thus takes different forms; it is imagined and experienced in contrasting ways, in social settings that change over time. It is a variable, lifelong process, intertwined with the life-courses followed by contemporaries and by earlier and later generations. This chapter now

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explores impacts on ageing made by a key feature of contemporary change—globalization—before interrogating theories of ageing and their impacts on the ways in which different aspects of ageing can be explored sociologically.

Global(ized) ageing: migration, cultures, policies, and perceptions

Examining ageing in global terms underscores the contrasting statuses, constraints, opportunities, and expectations associated with being ‘old’ in different societies. And contemporary globalization itself, with its accentuated levels of social and economic interdependence and its distribution of work and workers beyond national boundaries, has heightened ‘explosive’ degrees of inequality (Beck, 2013). As Hyde and Higgs (2016: p. 1) put it, while now ‘most people throughout the world can expect to live into their 60s and beyond’, that world has also changed—while it has grown wealthier, it remains profoundly unequal, and for vast numbers of older people, it remains extremely precarious. While there are declining opportunities for traditional forms of employment through which older people in the past tried to protect themselves, global markets and neoliberal policies portray as a luxury the social security spending protecting those in later life (Dorling, 2015; Macnicol, 2015).

Efforts to evade precarity produce global migration paths, stretching family networks and life-courses between continents. Older people may be left without family carers in their place of origin or migrate to new destinations and grow older there, contributing to the cultures of their new societies but affected by local cultural tensions and inequalities in social structure (HelpAge International, 2000; Yeates, 2005). Thus, ‘global care chains’ can arise in which:

an older daughter from a poor family ... cares for her siblings while her mother works as a nanny caring for the children of a migrating nanny who, in turn, cares for the child of a family in a rich country.

(Hochschild, 2000: p. 131)

Such ‘care chains’ impinge on the staffing of nursing homes, an industry that, in the United States alone, employs more people ‘than the auto and steel industries combined’ (Folbre, 2002: p. 186). This brings together two potentially vulnerable groups—older people and migrant, often female, workers—and adds the potential for cultural and linguistic strain to dangers of financial exploitation (Walsh and O’Shea, 2010). These strains may be accentuated by changes in family structures in nations with decreasing numbers of children. In Japan, for example, a need is growing for migrant labour to provide elder care; this does not sit easily with traditional attitudes to immigration (Powell, 2011: p. 47). In Austria, Weicht (2015) describes how foreign carers for older relatives are interpreted by families in contradictory ways—describing them as ‘angels’ applauds, but at the same time objectifies, them.

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'Host' nations may receive 'waves' of migrant workers from different origins; the circumstances and lifestyles associated with ageing in their countries of origin may differ from possibilities available in their new settings (Wingens et al., 2011). In the UK, Bangladeshi migrants, among others, may feel torn between appreciating economic survival and health support and, on the other hand, wishing to maintain ideals of family belonging vis-à-vis relatives many thousands of miles distant. Attitudes to space and place have become 'underlain by deep feelings of rift and division' (Gardner, 2002: p. 220). Silverstein and Attias-Donfut (2010: p. 185) argue that:

older adults who migrate to new international locations with, or following, their adult children, often lack the linguistic and cultural capital to integrate fully into their new surroundings and consequently suffer from loneliness and depression.

These are complex phenomena with mixed, and sometimes contradictory, impacts on individuals. A proportion of UK older people have chosen to live abroad for their retirement, rather than live in nursing homes (Warnes, 2009), but they may regard these choices differently as they age and as political circumstances change. A new research agenda now explores how family dynamics may stretch across continents, with ties and networks maintained or lost (Baars et al., 2017; Phillipson, 2010).

Globalization itself can have highly stratified effects on older generations (Estes and Phillipson, 2002). Welfare-state and other forms of social support have become precarious, not least where governments and employers embrace neoliberal policies, partly in response to expectations from global institutions. Older people may more often be expected to manage their own financial protection in age, though under conditions of heightened insecurity (Phillipson, 2009).

In such circumstances, cultural resources may either exacerbate or mitigate their predicaments (for a selection of such resources, see Sokolovsky, 2008). Fox (2005: p. 482), for example, seeks 'to illuminate the active, constructive work' older people do 'to find ways to age in their culture' (Fox, 2005: p. 484), contrasting Thailand with Australia. In the strongly Buddhist context of Thailand, filial care is experienced as a 'normative expectation'; in Australia, views of the life-course are much less strongly related to religious values, and older people in nursing homes may see care as 'a service to be provided in a professional manner' (Fox, 2005: p. 493). In divergent ways, social settings offer cultural resources affecting ageing (Torres, 2011), here enabling recipients of care to ascribe themselves a measure of autonomy, rather than perceiving themselves solely as dependent.

Cultural responses form part of the broader impact of sociopolitical factors on ageing, reflected in survival rates in different national settings, which are far from uniform internationally. In contrast with, say, Japan, until 1990, figures for the Czech Republic and East Germany were very

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low. After the fall of the Iron Curtain, rates for the Czech Republic remained modest, but East Germans, inhabiting a transformed sociopolitical context, have now caught up with West Germans. In the United States, in contrast, the rising trend is less certain—survival rates for the oldest women are not improving at all (Rau et al., 2008: pp. 757, 764–5), and life expectancy *fell* in 2015 (Kontis et al., 2017). The oldest forms of ageing can, in principle, become healthier. But trends do not continue automatically; they are affected by social circumstances and public policy decisions.

Thus, Christensen et al. (2009) stress that what used to be seen as objective ‘ageing processes’ are ‘modifiable’ through policy choice. They stress capacities to live both longer and better—‘most evidence for people aged younger than 85 years suggests postponement of limitations and disabilities’, despite increases in chronic conditions (Christensen et al., 2009: p. 1204). They attribute this to progress in factors such as housing standards, transport, education, gender roles, and social attitudes to disability; overall, 30–40% of people in their nineties live independently (Christensen et al., 2009: pp. 1204–5). Lubitz et al. (2003) show that although older people aged 70 have a longer life expectancy if they are in better health than if not, this need not necessarily mean that their total health care requires more expenditure. Improving the health of middle-aged populations could, in principle, enable them to live longer without costing health services more (Evans et al., 2001).

Here the globalized politics of economics impacts on local forms of ageing through affecting both action and inaction in national policies. Estes and Phillipson (2002) point to globalized policies actively undermining institutions protecting older people, for instance by favouring privatization in elder care. Such policies penetrate directly to individual level. If profit-driven forms of elder care invoke accountancy based rigidly on time spent on particular tasks, for instance, informal practices in care homes change, diverting time away from casual, but friendly, everyday practices that are crucial in making residents feel at home. Conversely, longevity is affected by factors associated with race and education, especially both combined; the survival rates of less educated black Americans are little better than 50 years ago (Olshansky et al., 2012). Yet overtly egalitarian policy changes are discouraged in a neoliberal global policy climate.

Since modes of ageing are so responsive to context, portraying ‘global ageing’ as a problem *in itself* is a vast oversimplification:

Alarmist demography and gerontological knowledge came together in the social surveys of the late nineteenth and early twentieth centuries that decried the growth rate and poverty of the elderly generation as an economic and moral crisis.

(Katz, 1996: p. 69)

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There are reasons for assuming that the global population will not simply develop exponentially into the future (Samir and Lutz, 2017), but 'alarmist demography' depends heavily on producing 'calculations' where age and 'dependency' are conflated. Global dependency ratios are themselves a form of social perception, 'measured' by counting proportions in a population who are (say) below 15 and above 65 years of age. This assumes, counterfactually, that all those in between are gainfully employed. It omits people who may be disabled and those on 'home duties'. It also equates 'dependency' with not earning a monetary wage, ignoring other forms of social input such as childcare or mutual care among family members or neighbours. This has the political effect of erasing perception of a wide variety of forms of social support and citizenship. Bytheway (2011: p. 173) points out that people who are economically employed also 'depend' on older people (and children) for unpaid domestic and caring work. Lastly, it assumes that productivity rises and falls simply according to the numbers of people in employment, which is not the case.

McGee (2002) contends for Canada that even if crude calculations of 'dependency' are made on the basis of age alone, dependency ratios are not necessarily rising. Macnicol (2015) shows that the so-called 'old-age dependency ratio' in the UK is counterbalanced by decreasing numbers of children. According to Spijker and MacInnes (2013), even if we define people as 'dependent' when they have 15 years or fewer to live, the 'dependency ratio' has fallen by a third over 40 years; the total proportion of people in work in the UK (now 48%) has barely changed since 60 years ago, when it was 46%. In any case, as Macnicol points out, assuming that *young* people can easily access productive employment is highly questionable at a time of rapid changes in the world of work. Using age ratios to generate 'moral panic' thus amounts to an 'ageist' campaign against older people, which itself demands analysis from a sociological viewpoint. Calculations about global ageing may *appear* objective, but they depend on decisions about what needs to be counted and how that exposes deep-rooted contestation about how the life-course itself is regarded.

Perspectives on ageing: theories and stances

Seeking insight into different facets of ageing, sociologists have explored not only its social circumstances, but also the discourse about ageing itself—including their own past and present debates. The wish to avoid, suppress, or disguise ageing can be accentuated by the 'social imaginaries' of the time—that is, the underlying

ways in which people imagine their social existence, how they fit together with others, how things go on between them and their fellows, the expectations that are normally met, and the deeper normative notions and images that underlie these expectations.

(Taylor, 2002: p. 106)

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Achenbaum (1995) stresses that the development of academic attention to ageing, just after World War II, occurred at a time of flight from trust in politics towards faith in science as a harbinger of progress. This accentuated the 'biomedicalization' of ageing (Estes and Binney, 1989), in which ageing is perceived not just as a problem, but as a medical problem. The 'anti-ageing' movement remains an attempt to 'cure' it through biomedical means.

Since ageing has so many dimensions, from its physical parameters to the ways it impinges on experience, sociological theories of ageing are constantly developed and adjusted in efforts to capture evolving interactions. They also reflect developing accents and methods within sociology itself (Bengtson et al., 2009; Phillipson and Baars, 2007). But underlying reasons for adjustments in the theoretical approach embody conflicting views on social causality—how social structures and power affect an individual's agency, and vice versa—and the locus of responsibility for life-course events. Theoretical stances differ in terms of how they take account of these complexities and in terms of the extent to which they endorse critical stances vis-à-vis social impacts on ageing (cf. Biggs et al., 2003).

An early attempt to theorize ageing, the 'disengagement' approach taken by Cumming and Henry (1961), adopted the functionalist analysis common among sociologists at the time. The authors envisaged separate sections of society in terms of contributions to the 'functioning' of the whole, seeing individuals' ageing as adapting to changing functions over the life-course. Ageing and retirement represented the secession of older generations from productive social roles, making room for younger ones. Their work attracted objections for methodological reasons, but its moral and political implications *for individuals* caused particular contention. Cumming and Henry were read as accepting that people of retirement age are of negligible social importance and ignoring the meaning of older age to individuals (Hochschild, 1976).

The career of disengagement theory illustrates the slippage between theories of how social ageing arises and prescriptions for individuals' own ageing. In contrast to Cumming and Henry, 'activity theory' (Havighurst and Albrecht, 1953; Havighurst et al., 1963) focused on positive social 'roles' played by older people, for instance in grandparenting or belonging to a church (cf. James et al., 2006). Identifying such contributions seemed to adjure older people to keep involved and energized, using leisure time creatively. Relatedly, the 'continuity' approach to ageing (Atchley, 1989a: p. 183) saw maintaining continuity with past subjective and social experiences as 'a grand adaptive strategy', by which individuals can defend themselves from structural disadvantage and ageism; this was interpreted as advice for preserving individual identity over time (Atchley, 1989b; cf. Nuttman-Shwartz, 2008). These positions share three features. All contain prescriptive elements; all have implications on the micro- as well as the macro-scale, with individuals expected to bear the burden of problems stemming from social

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structures. And each contains observations that are convincing in part —‘disengagement’ applies to some people in some circumstances, while supporting ‘continuity’ of lifestyle for, say, nursing home residents has considerable appeal. As heuristics directing attention in research practice, though not as universal accounts of ageing, each has productive potential.

Theories of ageing thus vary in terms of their scale, prescriptiveness, power, and views of social determinism. Modernization theory (Cowgill, 1974), for example, contends that industrial societies devalue the experience and knowledge of earlier generations, impressed instead by fast-changing new skills associated with younger people. This position too has been criticized as unduly universalistic, homogenizing multiple different experiences and situations, as well as idealizing the position of older people in earlier, rural societies. We might add that its large-scale imputations are heavily inspired by induction from individual experience, though certainly it sometimes seems convincing. This applies too to exchange theory, which connects older people’s social status to resources they can offer others (Dowd, 1980). Though older people’s social resources may seem depleted from an ‘exchange’ viewpoint, in the semi-traditional rural society of Ireland in the 1930s, to give one example, many (especially older men owning farms or small businesses) did possess powerful resources in terms of others’ life-courses, with status to match (Arensberg and Kimball, 1940/2001). In contrast, ‘age stratification theory’ interrogated more varied types of social pressure on behaviour, identifying roles prescribed for people in different age ‘strata’ and the ideological pressures involved, while at the same time it advocated resistance to such pressures (Dannefer et al., 2005; Riley and Riley, 2000).

These contrasting approaches cumulatively stress how strongly social processes affect ageing at all levels. Increasingly, therefore, possibilities for influencing these processes were explored. The ‘political economy of old age’ (Estes, 1991) focused on exploring state decisions about distributing economic resources among different age groups—in effect creating forms of ‘structured dependency’ (Townsend, 1981: p. 77). Inequality in old age needed to be understood at least partly in terms of socio-economic processes tending to marginalize older people (Walker, 1981, 1996). They should not be regarded as a homogenous group defined in terms of chronological age, for their different problems had different causes, to be tracked empirically. Poverty among older people resulted from their labour-market positions and subsequent exclusion from it, or from low levels of social benefits. Ageing in any given society was fundamentally affected by the economy, state, and employment, but also by class, gender, and ethnicity. This approach harnessed interdisciplinary resources to explore such impacts on ageing under the aegis of ‘critical gerontology’ (Phillipson, 1998).

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In this tradition, H.R. Moody (1988: p. 32) argues that gerontology itself should offer an 'emancipatory discourse', with 'a positive idea of human development: that is, ageing as a movement toward freedom beyond domination (autonomy, wisdom, transcendence)'. Thomas Cole (1992: p. 237) too contends that analysing ageing in purportedly technical terms amounts to a moral and political position in itself, relegating ageing to a (futile) attempt to evade disease, rather than confronting 'conflict, mystery and suffering in late life'. Thus 'ageing' is an irreducibly moral concept. This 'humanistic' understanding of ageing includes explicating how moral positions are generated, endorsed, or precluded by particular social constellations. Theories of 'moral economy' show that social norms, for instance prescribing obligations we owe each other within families or between generations, are themselves influenced by political economies of ageing (Kohli, 1987; Minkler and Cole, 1991). Public views on the desirability of certain ways of behaving reflect ideas about power and justice, not least justice between generations. To what extent should older generations sacrifice their interests for those of younger ones, or vice versa?

Stress on society-wide phenomena needed counterbalance where variations were explored among forms of ageing and their social settings. Hareven (1984) opposed seeking linear patterns of development in accounts of ageing, given the differential impacts of race, class, family form, and ethnicity on intergenerational relationships in different times and circumstances. Using the adaptation of Schutzian phenomenology introduced by Berger and Luckmann (1966), subsequent accounts of ageing stressed 'the social construction of reality'—the impact of social practices on how ageing and older people are envisaged, and how their opportunities and constraints evolve. Constructionist forms of analysis disentangle everyday interactions to track how daily practices and 'unwitting routines' build up worlds of experience (Gubrium 1997: p. 1) which partly interlock and simultaneously diverge. People may, for example, use common narratives to perform different functions in the ways they attach meaning to their ageing and that of others (Gubrium, 2011).

Such interpretive efforts by no means entail a relativistic approach to the philosophy of science. Most sociologists of ageing show an assiduity in seeking optimal forms of evidence and argument that is implicitly compatible with critical realism (Sayer, 2000) in respect of their views about the empirical world. Thus, Corner and Bond (2006), discussing effects of the diagnosis of 'mild cognitive impairment', point to potent social effects of applying this 'label' to older individuals—they may both be treated differently and come to regard themselves differently as a result. As Phillipson's exposition of critical gerontology stresses (Edmondson and von Kondratowitz, 2009; Phillipson, 1998), this means attending to *both* economics and power *and* meaning and the social processes by which it is created and changed.

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The variety of approaches summarized as 'cultural' gerontology thus accentuate attention to social origins of meaning and experience, and their effects on ageing in contemporary societies. Stories and images relating to ageing (de Medeiros, 2014; Hepworth, 2000) cast light on the ways in which people develop a sense of who they are as they age and how older people are seen by others. This ascription of cultural meanings profoundly affects people's experiences, even of their own bodies (Katz, 2002); culture, in other words, involves power (Andersson, 2002; Tulle, 2008). Yet exploring the operation of symbolic processes in practice can also draw attention to the dialogical nature of human experience (Biggs, 2004) and older individuals' capacities to use social meanings in creative ways. Blaikie (2002) argues that, as an alternative to cultures of 'consolation' or 'incorporation', older individuals can adopt 'cultures of resistance' to homogenizing social processes. For Kunow (2009), the 'transformative power' of ageing sometimes depicted in the literature highlights special forms of resistance, in which older people may reach heights of courage they were unable to attain at earlier life stages.

Such work signals eagerness to underline the potential for older people's active intervention in their own predicaments. Gilleard and Higgs (2000) and Rees Jones et al. (2008: p. 1) view consumption, what people buy, not as a mere side effect of work, but as possessing 'a significance of its own'; they see modern retirees not just as 'pensioners', but as 'a putative leisure class'. They explore whether at least some older people can situate themselves powerfully in society, with heightened resources for defence against ageism, profiting from bodily appearances that are socially acceptable and health and resources enabling them to engage in leisure activities formerly associated with younger generations. This approach potentially modifies Mannheim's earlier work on generations, not seeing them as discrete, opposed horizontal groups, but postulating that succeeding generations both take with them elements of previous generations' views and contribute new, contrasting habits and behaviour.

Reference to 'generations' connects sociological approaches to ageing explicitly with conceptions of time (Baars, 2012). Elder (1998) stresses that trajectory over time gives their form and meaning to life-course transitions; 'life-course theory' tracks intertwining trajectories that intersect through individuals' lifetimes, both responding to social contexts and affecting them (see Wingens et al., 2011 for a life-course approach to ethnicity). Early work in this tradition deployed biographical methods to yield insights into the life-worlds of people living out comparable trajectories, notably artisan bakers in France (Bertaux and Kohli, 1984). Bengtson et al. (2005: pp. 493-4) stress the life-course approach's potential not only to explore 'linked lives' within cohorts and between generations, within their historical contexts, but also to highlight 'agency and the idea that planfulness and effort can affect life outcomes'. People may be profoundly affected by the same overall historical circumstances but react differently to them in lasting ways (Elder, 1974).

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In practice, life-course analyses have offered a range of positions on the issue of what freedom individuals have to affect the course of ageing. Kohli (2007: p. 254), for instance, sees the life-course approach as focusing 'on the patterning of time in the various life domains', intended to result in 'an account of the *longue durée*'—the way 'typical' life-courses have changed as between pre- and late-industrial societies in the West, pre-eminently in response to changes in the structure of work. This analysis sees 'the experience of the temporality of life' as 'a feature of an evolved structural order' in which individuals move through sequences of social positions, prescribed to them via rules and norms in succeeding historical settings (Kohli, 2007: p. 255). Questions concern the role of 'individualization' in contemporary societies and the extent to which it 'frees' individuals from 'the bonds of status, locality and family of origin' (Kohli, 2007: p. 255)—or, on the contrary, merely exposes them to larger-scale social pressures.

Longitudinal data collected across national settings yield material tracking life-courses across ever larger numbers of birth cohorts, adding information on the strong input of state decisions to life-course developments (Mayer, 2004, 2009). Attempts can be made to isolate relatively stable socio-economic characteristics and behaviour, as well as interactions between life stages; how 'set' are trajectories by early life circumstances? 'Can events and conditions in adulthood significantly alter further trajectories and outcomes?' (Mayer, 2009: p. 417). Laub and Sampson (2003) contest assumptions of childhood determinism, but Mayer (2009: p. 423) underlines the continuing nature of this debate. Brückner and Mayer (2005) warn too against imputing overall unidirectional trends to entire societies—some social patterns may be 'destandardized', but others are not. Using half a century's data for West Germany, they confirm 'de-coupling' between trajectories of family formation and those of school, training, and work (Brückner and Mayer, 2005: pp. 48–9). But women's life-courses have converged with men's in terms of education and participation in the labour force, in that respect increasing life-course *homogenization*. This is not to deny that social structures generate inequalities that accumulate not only through individuals' life-courses, but also even between generations (Ferraro et al., 2009).

These analyses of ageing and time are complemented by accounts derived from the work of Foucault (1978), stressing relations between power and discourse that extend deep into the ways individuals internalize structures of control, through to their experiences of their own bodies. A Foucauldian approach to 'biopolitics' explores states' efforts to monitor and control citizens' life processes, from birth to death, supported by the power of 'experts', and the corresponding framing of older people as 'dependent' (Powell, 2006: p. 98ff). Foucault sees elements of social life otherwise supposedly exceptional, such as the constant surveillance exercised in prisons, as core to processes involved in social power and control (Tulle, 2008). Thus, Katz's work on *Disciplining Old Age* (Katz,

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1996) interprets the rise of gerontology itself at a particular historical juncture in terms of Foucauldian patterns of control.

Time is necessarily central to accounts of ageing (Baars, 2012; Edmondson, 2015). Constructionist approaches to time explore how interaction and talk *produce* changing realities among which people negotiate as they age. They may, for instance, disclose how retirees struggle between alternative directives for the future, torn between socially powerful 'busybody' ideals of active life versus solidarity with vulnerable older people (Lundgren et al., 2018). By describing and reacting to age-related phenomena as we do, we help them to be that way (Gubrium, 2011), producing identities via the narratives we choose (de Medeiros, 2014).

Welfare states and changing societies

The circumstances and experience of ageing, and the ways it is socially conceptualized, represent entwined patterns of advance, regression, and unintended consequences. Support from welfare states has saved millions from the rigours of poverty affecting older age, but because work has become a dominant source of status, preventing them from working also marginalizes older people.

Bismarck's efforts in connection with old-age pensions in Germany after the 1870s represented an attempt to curtail ills associated with developing industrialism, social problems with which families, neighbours, churches, and private charities could not cope. As Thane (2005: p. 9) emphasizes, past societies often contained large proportions of older people—'At least 10% of the populations of England, France and Spain were aged over 60 even in the 18th century.' But their lives were often precarious, even miserable, particularly if children did not survive to adulthood or moved to far-flung locations in search of work. While industrialization initially affected many older people for the worse, capacities for enacting larger-scale social policies had also expanded and could be used with the aim of protecting them.

It was therefore to be expected that older people should depend more than most other 'groups' on welfare states for economic and health security (Komp and van Tilburg, 2010)—but in a range of ways. Those most likely to be economically vulnerable in older age include older women, members of minorities, and those with lifelong low incomes. When older people become poor, they are likely to remain so in the absence of state intervention (Scharf, 2009: p. 45). But contrasting forms of welfare state provision affect citizens differently (Motel-Klingebiel, 2006). Esping-Anderson (1999) suggested distinctions between welfare regime types, according to the relative responsibility allocated to markets, states, and families. Liberal welfare states, such as the United States and the UK, provide means-tested benefits to a limited extent; socio-democratic regimes, such as Norway and Sweden, offer higher benefits (currently under modification); conservative-corporatist regimes,

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such as Germany, France, and Italy, offer benefits on insurance principles; 'Mediterranean' regimes, such as Spain, are in the process of evolving away from 'residualist' systems whose major reliance for older care rested on the family. While such structures impact differentially on social relationships, particularly between older individuals and their families, these impacts are not always those anticipated (or feared). Motel-Klingebiel *et al.* (2005), on the basis of a five-country study, rebut suspicions that welfare states 'crowd out' family relationships. They do not automatically cause families to withdraw from elder care, abdicating responsibility to the state. As Künemund and Rein (1999) had predicted, high volumes of state help may encourage family members to follow suit. Indeed, Daatland (2009) argues that developed welfare state provision offers opportunities for newly respectful and independent family relationships.

Relations between patterns of ageing and welfare states thus depend on complex blends of social attitudes and opportunities, not always apparent on the surface. Care for older people is often represented as a generational compact—those who are currently younger pay for older generations, assuming that they too will eventually be supported. This image can be misleading, seeming to justify later retirement as a matter of fairness. Macnicol (2015) shows that this measure, rather than relieving burdens on the young, depresses wages and weakens labour power. Moreover, welfare states rely on implicit *gender* contracts (Ginn, 2001; Ginn and Arber, 2000); the gender distribution of paid versus unpaid labour means that caring for children and older people tends to fall to the share of women. Women's unpaid work affects welfare systems directly, freeing men to work and assuming responsibility for those who are young, old, or sick. Ginn and Arber acknowledge welfare states' efforts to compensate for caring over the life-course, but this cannot outweigh the results of employment patterns. Especially if they are members of ethnic minorities, women's employment records are likely to involve part-time work or include breaks for family-related reasons. Thus, reducing public pensions in favour of private and occupational ones accentuates gender inequality in later life.

Christensen *et al.* (2009) suggest that if, in future, people are permitted to choose to work to later ages, this could involve more part-time employment, part of a pattern of the 'redistribution of work' (Christensen *et al.*, 2009: p. 1205). This could, they argue, benefit both genders and all generations, militating against the effects of 'long hours' work cultures on families. Yet this suggestion could be hard to realize in a climate where individuals are expected to save for their own old age, itself unrealistic in low-interest, technically complex financial regimes. While, in the very recent past, it was possible for individuals with modest career trajectories to fund their own eventual nursing-home care, in many countries, owing to mounting costs, this is no longer feasible, even for those with substantial pensions (the international variations here illustrate the impact of public policy on care regimes). This change has had an impact

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on the ways the life-course is both envisaged and experienced that is seldom acknowledged—planning for contingencies in one's own old age has become impossible for many people. Older people may in any case experience multiple precarities in older age (Lain et al., 2019). What Hacker (2006) describes as a 'shift of risk' from institutions to individuals has undermined many twentieth-century advances in sharing risks that are too great to be borne individually.

Generations and gender

Welfare state support for older generations emanates from resolve to mitigate the insecurity to which old age has, throughout history, been subject (Hudson, 1999; Walker, 1996). In popular opinion, the support for older people on which this is based seems relatively intact (Frommert et al., 2009). In any case, Albertini et al. (2007), among many others, stress that, taking account of all forms of financial transfer between generations, including family transfers, older generations give more to younger ones than the other way round, contributing actively to local economies throughout their whole life-courses.

Attias-Donfut and Arber (2000) explore the many different uses of the term 'generation' itself, blending different approaches to historical timing and periodization and to the genealogical rungs of family ladders. Bengtson (2001: p. 8) posits six interacting dimensions of intergenerational relations, distinguishing affectual and associational measures, and consensual, functional, normative, and structural forms of solidarity. Contemporary generations also share more years together than in the past (Hank and Buber, 2009). The term 'the Third Age' denotes the active later lives that now healthier older generations might anticipate, with new impacts on families and society (cf. James and Wink, 2007; Laslett, 1987). The notion of the 'Fourth Age' arose as a counterbalance, indicating an eventual period of infirmity remaining unavoidable for some. Sociologists such as Haim Hazan (2009) warn against imposing demands for 'successful' ageing and 'positive' forms of conformity on this period of life especially. Cavalli et al. (2007) confirm the importance of health in transitions between these life 'stages'—it is in response to declining health that the octogenarians they study disengage from social interaction with family and friends, rather than life events such as the loss of relatives or entering nursing homes. Social choices supporting older generations' health thus remain key to their future capacities for well-being, but much work remains to be done to understand and support the 'Fourth Age' and the processes surrounding death (Higgs and Gilleard, 2015).

Arber and Ginn (2005: pp. 527–8) point out that the numerical domination by older women over older men is now diminishing, as survival rates begin to converge, but the 'feminization of ageing' is still marked by women's systematic disadvantages under current social conditions, not least with regard to pensions, health, and access to care (Attias-Donfut and Arber, 2000). Even marriage affects the genders differently. If older

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men are widowed, they tend to remarry; thus, most older men have partners for 'companionship, domestic service support and care should they become physically disabled' (Arber and Ginn, 2005: p. 529). But nearly half of women over 65 are widowed, and over four-fifths at 85 and over; in consequence, many more women than men live in nursing homes (Arber and Ginn, 2005: p. 531). Older women in Europe and the UK are more likely to be poor, owing both to family (child-) care patterns and the prevalence of part-time work during their working lives (cf. Arber et al., 2007).

Gender relations are thus entwined with power relations, suffusing cultural attitudes and images (Bernard et al., 2000). Older women's experiences derive, in part, from expectations about their social presence and roles; discourses about gender are entwined with those about age, and the two sets of expectations can reinforce each other (Krekula, 2007; Wilińska, 2010). Much work on women and ageing centres on the body and how women feel pressured to present themselves—the ways in which social identities are constructed and contested through choices and conventions involving clothing and other aspects of appearance (Twigg, 2012; Ylänne, 2012). Susan Sontag's observations are still quoted on the absence of public dignity and status for older women (Teuscher and Teuscher, 2007):

Growing older is mainly an ordeal of the imagination—a moral disease, a social pathology—intrinsic to which is the fact that it afflicts women much more than men. It is particularly women who experience growing older ... with such distaste and even shame.

(Sontag, 1972: p. 30)

If this is often the case, it does not preclude variations. In societies including the UK, older women's comparatively prominent role in supporting kin, though it imposes obligations, offers compensations (Finch and Mason, 1993; Wenger, 1987; Young and Wilmot, 1957). Nonetheless, being female and experiencing social exclusion in ageing continue to go together (Carney, 2017). This applies too to intersectional social divisions affecting LGBT older people (Cronin and King, 2010), subject to interacting forms of disadvantage and exclusion (Giunta and Rowan, 2015). Many of these can be addressed by community support (Hughes, 2016) and a reduction of heteronormative bias. Bias has affected studies of older men too, significantly by assuming their support for communal life is negligible, which is often not the case (Davidson et al., 2003). In Ireland, Timonen et al. (2011: p. 58) report that men older than 75 are more socially integrated than women of a similar age. This underlines men's contributions to community and care; it may sometimes attest to the old custom of 'visiting', 'rambling', or 'bringing the chat' among men, when Ireland was still a semi-traditional society. Health-related and cultural changes also impact on age and gender roles. In Africa, traditional expectations of older people centred on spiritual roles such as ensuring communal harmony; many such expectations are

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currently being shattered, not only by the impact of human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) on parental generations, leaving the responsibility for children on grandparents' shoulders, but also by the effects of westernized modernization (Nhongo, 2004).

Environments, families, and mutual care

Diversity in life-courses reflects variations in the environment, but in ways whose effects may differ from those anticipated. Rural settings in particular are often pictured as offering excellent surroundings for later life, but this overlooks a variety of possible exigencies, including poverty, isolation, and local social decline (Edmondson and Scharf, 2015; Keating, 2008). Rozanova et al. (2012: p. 25) acknowledge claims of 'positive associations between social engagement and well-being in later life' and that older people participate intensely in rural communities, but they underline the need to explore what type of participation is involved and how freely it is given. Rural areas may support specific forms of 'social capital', but these, however significant in their own terms, may not necessarily take liberal, democratic forms. Older people in the countryside may be respected for their knowledge and skills, an effect enhanced among groups familiar with the older individuals in question and to whose lives their achievements are relevant, as in music or sport. To what extent does this depend on rurality as such? Gallagher (2008) found that in Ireland—where the distinction between rural and urban areas remains relatively fluid—patterns of mutual social support among older people in Dublin and those in the country were surprisingly similar. Neighbourly relations and local networks and sharing the social landscape with familiar others contributed markedly to older people's lives.

Such phenomena help explain the common desire to 'age in place', now recognized in much social policy for older people. But Sixsmith and Sixsmith (2008) point to possible complications—the homes in which individuals have grown old may no longer be easy to inhabit, for reasons ranging from their physical structures to their locations (cf. Means, 2007). Environmental gerontologists explore complex interactions between social and physical elements of place in relation to older people (Andrews and Phillips, 2005; Peace et al., 2005), examining how settings come to be 'enabling' or 'disabling' to those who live in them (Smith, 2009). Older people with different needs may wish to age in place but require different sets of provisions there (van Dijk et al, 2015).

Environments are, in part, experienced through the medium of family structures and expectations, which themselves are changing in contemporary societies, though Bengtson (2001) insists that this does not make them less important. Multigenerationality and the role of grandparents in caring for grandchildren may be growing more significant, as grandparents survive longer. Families are often 'long and thin', 'beanpoles' (Bengtson et al., 1990), rather than networks with large

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numbers of siblings and cousins at each level. Bengtson stresses that there is great diversity across family practices and no entirely dominant type (cf. Matthews and Sun, 2006). Amid fears for the overall 'decline of the family', Stacey (1996) argues that diverse, 'post-modern' family forms have become normal. Normality does not entail freedom from all stress. Harper (2013) suggests that forming new sets of relationships in 'patchwork' families may be complex and challenging, but the impetus towards family solidarity continues nonetheless.

Fluid family forms do not automatically increase social and familial isolation; in principle, they may make more relatives available to individuals in modern societies. Uhlenberg (1996) calculates that, for children born in 1900, the chances of being orphaned before the age of 18 were 18%, and by the age of 30, only 21% had any grandparents still living. But for children born in 2000, 68% will have four grandparents still alive by the time they are 18. Today's 20-year olds are more likely to have a grandmother living than 20-year olds in 1900 were to have a mother. The social implications of such changes are diverse. As Hareven (1984) indicates, transitions in individuals' life stages at the start of the twentieth century depended not only on their own circumstances (for instance, waiting to find work before it was deemed possible to marry), but also on the circumstances of their families—marriage might be delayed by the obligation to support dependent kin. There followed a period in the mid-twentieth century when transitions were expected to conform to general norms; for example, only after marriage would people aim to have children. Such patterns are now re-forming. Where, in the nineteenth century, families were disrupted and reconstituted as a result of deaths, this now occurs via factors such as divorce and remarriage.

It has often been assumed that family forms contrast between the north of Europe, seen as more individualistic, but more inclined to favour social care, and the south, seen as more familistic, relying heavily on family care owing to a dearth of effective social services. This was interpreted as indicating weaker family ties in the north (Reher, 1998). Dykstra and Fokkema (2011) contest this, arguing that each of four family patterns is fairly common throughout European countries. They postulate two 'familistic' forms, both characterized by members living close to each other, with frequent contact and acknowledging norms of family obligation. In 'descending' forms, help in kind is given more by parents to children, whereas in 'ascending' forms, more help in kind is given by children to parents. Then there are 'supportive-at-a-distance' families in which members neither live nearby nor follow obligation norms, but do have frequent contact, with financial support given mainly by parents to adult children; and 'autonomous' families where members neither live in proximity nor acknowledge obligation norms or engage in frequent contact or assistance. Dykstra and Fokkema argue that 'autonomous' families are not most concentrated in the northern nations, which instead show high levels of 'support at a distance'. They found high levels of autonomy in France and Switzerland; autonomy was also likelier among

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families characterized by divorce and high socio-economic status. A single family might move through different patterns at various stages in the family life cycle—perhaps culminating in ‘ascending’ patterns when parents were most vulnerable. Families are developing *processes*, rather than fixed *structures*.

While family ties are crucial in ageing, particularly in terms of care and life satisfaction, more research is needed on other types of relationship too. Bengtson (2001) argues that friendships may support or even replace family ties (cf. Allan, 2010), although Sennett (1998) notes that many contemporary pressures militate against maintaining deep friendships. These include work- and life-course-related insecurities or professional pressures to move location continually, encouraging short-termism in personal connections. In western societies, more people are living alone in later life, as a result not only of widowhood, but also of choice—reluctance to enter nursing homes or a preference for ‘intimacy at a distance’ with family. In the United States, about a third of people over 65 live alone, and 40% of those older than 85 (Portacolone, 2015)—for reasons ranging from personal choice to isolation and precarity. In Northern Europe, some 50% of households consist of a single person, and the majority of women over 65 live alone (Jamieson and Simpson, 2013). This need not entail isolation. Ziegler and Schwanen (2011) argue that mobility, taking trips through physical space, enhances well-being via ‘mobility of the self’, willingness ‘to connect with the world and otherness, with people and places beyond oneself’ (Ziegler and Schwanen, 2011: p. 763). While it is sometimes argued that openness to experience decreases with age, Mühlig-Versen et al. (2012) suggest that appropriate contextual and personal resources can enhance it, as they do via volunteering work.

It is part of the stereotype of older people to picture them as lonely. In Sweden, nearly 90% of respondents may expect retired people to be lonely (Tornstam, 2007). In contrast, the highest rates of reporting feeling lonely ‘some of the time’ are found among young people, although those who say they feel lonely ‘all or most of the time’ do tend to be older than 70 (Victor et al., 2009). Victor and Bowling (2012) show that, in the UK, about 9% of people aged 65 and over say they are severely lonely, 30% sometimes lonely, and 61% never; loneliness can be assuaged not only by more social relationships, but also by improved physical health. The contributions of overall social circumstances to loneliness are underlined by the finding that it varies more by country than by age (Yang and Victor, 2011); forms taken by loneliness and loss vary too, according to social pathways connected with stigmatization, health, and social estrangement (Graham and Stephenson, 2010). Thus, Fokkema et al. (2012) find that older people in central and southern Europe are lonelier than those in the north and west, for reasons of singleness, poverty, and poor health. Contemporary researchers see loneliness as primarily based on having too few personal relationships or relationships, which is certainly significant. But it is possible to feel lonely when deprived of a social role

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or social meaning or of a cultural setting in which one can communicate one's own story or viewpoint, irrespective of the number of people one knows (Edmondson, 2015: p. 136). This argues for supplementing person-based analyses with sociocultural approaches to loneliness.

Older people themselves not only receive but also give care, both outside the family and within it, not least in terms of spousal care or grandparenting. In the contemporary world, about three-quarters will become grandparents at some time and will enjoy this status for longer than formerly. Hagestad (2006) explores grandparents' functions as 'supporting', 'saving', or 'rescuing' either grandchildren or their parents (often by enabling mothers to go out to work). Lüscher and Pillemer (1998) indicate the possibility of 'ambivalence' to grandparenthood, while Cherlin and Furstenberg (1986) describe detached, passive, supportive, authoritative, or influential styles of grandparenting. Yet Timonen and Arber (2012: p. 7) remark that such categories are 'not well suited to examining possible differences in how a grandparent relates to different grandchildren, and also overlook the possibility that grandchildren may exert an influence on the nature of the relationship'. They underline grandparents' roles in 'transmitting knowledge and values to younger generations', 'providing a sense of family heritage and stability', as well as influencing grandchildren's 'core moral values' and religious orientations (Timonen and Arber, 2012: p. 5). To the extent that women are expected to play more active roles than men in sustaining family relations, they may be 'more likely to become key figures in young grandchildren's lives' (Timonen and Arber, 2012: p. 8). Thus, the impact of gender on family experiences of ageing remains salient. It is heightened in crisis situations such as those involving HIV/AIDS, when older women may be compelled to rise to heights of resilience and activity in defence of their grandchildren (Casale, 2011). This does not make intergenerational understanding automatic, for instance when individuals become extremely infirm (Hazan, 2011) or when the family is affected by divorce (Doyle et al., 2010), poverty, or unemployment. The complexities operating at earlier life stages do not disappear in later life, and it is questionable if sociology has entirely come to terms with this life phase, as seen from the viewpoint of those experiencing it.

Social exclusion and ageism

A variety of factors might enhance the possibility of 'ageing well', including good health, adequate material standards, good social relations, and an agreeable neighbourhood—not omitting less tangible factors admired in contemporary cultures, 'independence, control, and autonomy' (Bowling, 2005). How easy is it to achieve ageing like this? Poverty and class, in particular, construct perennial barriers, excluding individuals from activities that are otherwise accepted as normal (Abrams et al., 2007). Social pathologies, including ageism, sexism, ableism, and others, play parts in elder abuse (Walsh et al., 2010), as do institutional pressures such as stress (Schiamberg et al., 2011) or the socio-economic predicaments of perpetrators (Lowenstein et al., 2009). On causes of

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exclusion, rather than abuse, Scharf et al. (2005: p. 78) highlight a lack of access to material resources, income, security, social relationships, civic activities, and basic services. These diminish capacities to manage everyday life, affecting people's senses of self and quality of life, as do their immediate residential settings. Forms of exclusion can cluster in particular places, impacting on residents' self-definitions, as well as the ways they are regarded by other people. In some urban areas of England, over a third of residents are socially excluded according to two or more of these measures; health and ethnic origin play parts here, as does educational level (Scharf et al., 2005: p. 83).

In different ways in cities and in rural areas, older people's settings may be changing around them, accentuating feelings of being pushed 'to the margins' (Abbott and Sapsford, 2005; Burns et al., 2012); as they age, their own preferences may change (van Dijk et al., 2015). Public settings can enhance older people's senses of self and mastery of their environments (as when they can assume that personal encounters can take place safely in familiar public spaces) or diminish it (as a lack of public transport may do). The World Health Organization (2011) has urged 'age-friendly' cities to develop social and material structures to heighten fit with older adults' needs and preferences.

A further key issue is the exclusion of (older) people from *socially meaningful life activities*. This effect is particularly pronounced in societies where social status is intimately connected with work. To envisage ageing merely as not working is contemptuous of the value of human life, constraining older people's capacities to see meaning in their own lives (Edmondson, 2015), though Gilleard and Higgs (2000, 2005) point out that leisure activities may offer some counterbalance in terms of social participation. High levels of voluntary work indicate that many older people wish to remain active but demand some degree of control over what they do. In societies where agriculture remains significant, individuals in the lowest income quintiles, many of them farmers, may continue to work until late in life—as do people in the highest, such as doctors (Mosca and Barrett, 2011). Such whole-life avocations offer access to meaningful activity and respected social participation, but they are relatively unusual; more commonly, employment ends suddenly and retirement is associated with the feeling of exclusion (Fairhurst, 2003; Wetzel and Mahne, 2016). This may be accentuated by ill-health. In particular, people living with dementia have traditionally been subject to social exclusion, though current approaches to this condition contribute to appreciating the lasting value of human dignity and the capacities of older people to support each other (Weeks et al., 2012; Zimmermann, 2017).

'Social exclusion' refers to barriers from activities regarded as normal in a given society; 'ageism', a term introduced by Robert Butler (1975: p. 22), refers to 'systematic stereotyping and discrimination against people because they are old' (cf. Nelson, 2004). Stereotyping may be so ingrained that it is hard to avoid. Perpetuating stereotypes can itself

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'increase psychosocial risk factors for ill health', including a cascade of confirmation bias, self-fulfilling prophecies among professionals, and stress induced by being part of a group that is discriminated against (Golub and Langer, 2007: pp. 9–10). Ageist stereotypes can impact strongly where older people are vulnerable, as in care homes, where managerial style is crucial. Cooney and Murphy (2009) are not alone in finding that residents' capacities to exercise a modicum of control over their lives range from broad to completely minimal; Knight et al. (2010) highlight the positive effects that participation in care homes' decisions can have. Gallagher and Edmondson (2015) argue that care settings for older people can be transformed by committed and ethical forms of personal leadership.

While ageism is experienced as a problem in the population at large (Stuckelberger et al., 2012), the study of ageing itself is not immune to it. Though researchers claim to reject 'deficit' approaches to the field, questionnaires often assume that older people's activities focus on personal relationships and immediate settings, treating activities of broader social significance as of no interest to respondents. This is despite the fact that 'three fifths of men and women over 60 in Britain are members of one or more social, leisure, community, or religious group' (Arber et al., 2002: p. 91). On the basis of 117 articles published in *Ageing and Society* between 1997 and 2000, Bytheway (2002: p. 73) argues that 'much of our research is embedded in ageist assumptions about the societal implications of an aging population.' He revives Townsend's (1981) diagnosis of 'acquiescent functionalism'; Townsend later objected to neoliberal expectations pervading sociological analysis (Macnicol, 2015). These include undue stress on the virtues of independence, which affects older people themselves. Jolanki (2009) reports that respondents in Finland felt compelled to demonstrate how 'active' they were, fearing that otherwise they might not even count as competent moral agents.

For such reasons, Tanner (2010) urges 'learning from older people' how to support their strategies for negotiating bodily and external changes while attempting to 'stay themselves'. The sociology of ageing has developed emphases on the variety of transitions in later life (Grenier, 2012) and on minority experiences of ageing such as LGBT+ perceptions (Hughes, 2016), or migrants' experiences of the life-course (Ghorashi and Vieten, 2012). Enhancing older people's social participation, for instance in lifelong learning institutions, can illuminate and explore the benefits to society at large of older people's membership (Manheimer, 2005). Endo (2020) contends in Japan that older people's participation in community activities may come to militate against the work-based paradigm of human value. Yet, for Gullette (2017), such efforts are dwarfed by the scale of ageism, which, she argues, is all-pervasive. To overcome it, an entire cultural world needs to be dismantled, a world in which growing older is insidiously equivalent to decline.

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Life-course development, social meaning, and wisdom

It is a perennial complaint that social expectations fail to emphasize older people's contributions or make good use of their skills and capacities (Riley *et al.*, 1994). Bond *et al.* (1993) suggest that people grow more individual as they age, after long personal life-courses in specific environments; rather than concentrating on loss in relation to ageing, therefore, Levenson *et al.* (2001) argue for a 'liberative' approach to it. Many people attach importance to learning through, and from, their life-courses; McGee *et al.* (2011) find that older people in Ireland not uncommonly feel they have increased in wisdom and maturity. Glück and Bluck (2013) explore how individuals' handling of their cumulative life experience can contribute to wisdom. The question is how contemporary societies respond to this.

Older people's roles in relation to life-course meaning have traditionally been conceptualized in connection with religion, but Coleman (2009) argues that they face contradictory problems here. On the one hand, they are expected to transmit traditional views down the generations; on the other, they must adapt to change. Older people themselves may face religious problems and doubts—in which, Coleman reports, churches themselves may take surprisingly little interest. Dillon (2009), analysing life-course trajectories of older people born in California in 1929, tracks their personal responses to religious issues. She distinguishes between 'spiritual seekers', occupied with trying to work out spiritual meanings in their personal lives, and those who are 'religious' in the sense of belonging to religious communities or networks, attending church and participating in connected social activities. Such prescriptive settings can offer constructive social resources; Mehta (2009) examines varying approaches to managing their own ageing among ethnic groups in Singapore with allegiances to Confucianism, Islam, or Hinduism. Contrary to arguments that older people should be treated no differently from others, these world views prescribe appropriate modes of life and personal growth for particular life stages; these can enable rich and satisfying responses. Religion thus plays a variety of complex roles in later life, though finding appropriate languages for expressing and recording the trajectories involved poses a challenge for collecting evidence (Coleman, 2011).

Lars Tornstam's work on 'gerotranscendence' explores the increasing sympathy felt by some older people with 'transcendental sources of happiness' (Tornstam, 2005: p. 59), also often difficult to express in conventional language. Often, he says, 'The experience of nature evokes the feeling of being at one with the universe, which is called at-one-ment in the Eastern tradition'; 'small everyday experiences of nature', or the experience of having grandchildren, are felt as deeply significant, 'a way in which the barrier between the self and the universe is transcended' (Tornstam, 2005: pp. 59–60). Tornstam argues that his respondents show identity changes in later life, often achieving a less self-centred 'modern asceticism' and 'broadmindedness, tolerance and

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humility' (Tornstam, 2005: pp. 68–89). Achenbaum and Orwoll (1991) also focus on increasingly transcendent attitudes in comparison with more worldly aims in earlier life stages. H.R. Moody (2002) explores the holistic, transformational notion of 'conscious aging', and Schachter-Shalomi and Miller (1995: p. 5) stresses its 'service to the community'. Rothermund and Brandstädter (2003) support a 'mindfulness' approach to ageing, focusing on continual growth and change, with evolving criteria for what individuals think of themselves as obliged to do. Thus, McKee and Barber (1999) argue that wisdom may be developed in response to loss, potentially decreasing egocentricity and heightening empathy.

Caspari and Lee (2006) portray older individuals as offering wisdom, as well as broadening other generations' personal and social networks. Wisdom is studied, in many cases inspired by positive psychology, by authors including Sternberg (1998), Baltes and Staudinger (2000), Ardelt (2004) (see Ferrari and Westlake, 2012), and Grossmann et al. (2012), who explore the influence of American versus Japanese culture on wisdom among older people, impacting on their abilities to deal with conflict. Understanding wisdom also demands reconstructing the types of reasoning it involves (Edmondson et al., 2009), as well as its variety of social forms (Edmondson, 2005, 2009, 2013). Here it is possible to use ethnographic methods to track contrasting forms of wisdom-in-use, including complex engagements in ordinary social settings (Edmondson, 2015). These everyday versions of wisdom include the ways in which social interaction can heighten the insights of individuals who, on their own, might behave less wisely. Exploring older people's roles in such processes has potential for impacting on 'deficit' models of what the life-course involves, for both individuals and the societies to which they belong (Edmondson and Woerner, 2019).

Older people's interactions with their immediate environments and their neighbourhoods, communities, and societies help them form, maintain, and develop their roles and identities. These environments can be crucial sources of support in times of loss or transition; in turn, older people contribute decisively to them, in ways that demand further emphasis and exploration. Ageing therefore needs to be understood in terms of interacting practices forming 'social ecologies', in which mutual relationships change over time within layers of social and physical space and power. As people grow older, their relations to where and how they live may change, but becoming physically more fragile need not necessarily undermine them (Peace et al., 2005; Vincent et al., 2006). The fact that social structures, interpretations, and decisions so strongly affect these developments makes the sociology of ageing a reflection by society on its own processes and on the extent to which they support 'civic, cultural, educational, and voluntary engagement', as well as 'social and spiritual wellbeing' (Eales et al., 2008: p. 111), throughout the life course.

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Epidemiology of old age psychiatry: An overview of concepts and main studies



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Chapter:

Epidemiology of old age psychiatry: An overview of concepts and main studies

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This chapter has two parts—the first where we discuss some of the major concepts and methodological issues in the epidemiology of mental disorders in old age, and the second containing a summary of many of the most important studies in this field.

Epidemiology is the foundation of public health and rational planning of services. In the field of old age psychiatry, the information provided by epidemiological research has been highly influential. This chapter reviews the methods used and key population-based and combined studies that inform current thinking. However, this work is a dynamic process, as cohorts now and in the future may differ in relation to cultural, psychosocial, and medical factors, which need to be understood as we move forward in time.

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In this chapter, we present demographic data and emphasize the changes in the age distribution witnessed in the last century around the world. Following this, we cover some of the basic epidemiological concepts. Diving further into epidemiology and neuropsychology, we raise the burden of the neuropsychiatric disorders under the new demographic scenario, methodological issues in calculating epidemiological measures, and the diagnostic methods of identifying such neuropsychiatric conditions. We include a historical perspective and the evolution of the neuropathological findings of the dementias, as well as some of the most influential epidemiological longitudinal studies and combined studies that focus on old age neuropsychological conditions.

Part 1 Epidemiology and neuropsychiatric disorders in old age



Demographic transition

The world population is ageing, with extraordinary reductions in mortality and fertility rates. As a consequence of this 'demographic transition', the older population is growing proportionally faster than the other age segments. Indeed, the number of people aged 65 years and older has tripled over the last 50 years and will more than triple again over the next 50 years.

According to the United Nations, in 1950, 5.1% of the population were aged 65 years and over worldwide. In 2020, this is estimated to increase to 9.3%. In 2050, it is projected that 15.9% of people will be aged ≥ 65 years worldwide (United Nations, 2019). This demographic transition is a global phenomenon. It was first experienced by high-income countries (HICs), though it has recently been observed in low- and middle-income countries (LMICs) (United Nations, 2010). Although the proportion of older aged individuals living in HICs is higher, most (approximately two-thirds) of the global older population have been living in LMICs. The fastest-growing portion of the older aged population are persons aged 80 years and over. The projection for 2050 is that six countries will have more than 10 million people aged 80 years or over: China (101 million), India (43 million), United States of America (32 million), Japan (16 million), Brazil (14 million), and Indonesia (12 million). Taken together, they will account for 55% of all those aged 80 years or over in the world (United Nations, 2010).

To describe the age demographic transition, four phases have been defined. In the first phase, fertility was high, and populations grew slowly, even in the face of a high level of mortality. Periodic epidemics of plague, cholera, typhoid, and other infectious diseases would, in 1 or 2 years, almost wipe out the gains made over decades. Because overall both rates were in balance, population growth was typically very slow in stage one. Many human populations are believed to have had this balance until the late eighteenth century when this balance ended in Western Europe.

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The second stage begins when epidemics were better controlled and improvements to food supply and sanitation started to emerge. As a consequence, death rates dropped quickly, increasing life span. In Europe, the decline in death rates started in the late eighteenth century and carried on for approximately 100 years. As fertility remained high at first, there was an excess of births over deaths which led to population growth.

In the third phase, the imbalance between births over deaths was reduced as fertility rates dropped for a variety of reasons. These include, for example, access to contraception, urbanization, a reduction in the value of children's work, greater security for the older population, an increase in parental investment in the education of children, in addition to other social changes.

In the fourth stage, mortality and fertility are in balance again, but at lower levels. In some countries, such as Germany, Italy, and Japan, birth rates have dropped below replacement level, leading to shrinking of the population.

Fertility rates are now well below the replacement level in many HICs and in 31 LMICs. The level considered to ensure the replacement of generations is about 2.1 children per woman. Total fertility rate in HICs has dropped from 2.8 children per woman in 1950–1955 to 1.6 children per woman in 2005–2010. In LMICs the decline has started later, in the last three decades of the twentieth century, but has progressed faster. From 1950–1955 to 2005–2010, total fertility in LMICs dropped by over half, from 6.0 to 2.7 children per woman. However, great disparities between HICs and LMICs still persist (United Nations, 2010).

Life expectancy at birth has increased globally by 23.8 years from 1950–1955 (i.e. life expectancy at birth 47 years) to 2010–2015 (i.e. life expectancy at birth 70.8 years). The average gain in life expectancy at birth is 24.6 years in LMICs and 11.1 years in HICs (United Nations, 2010). HICs have experienced an epidemiologic transition, in parallel with their demographic transition. In the epidemiologic transition, pandemics of infection are replaced by degenerative, neoplastic, and man-made diseases caused by the adoption of unhealthy behaviours such as tobacco use, poor dietary habits, and a decline in physical activity. This transition has also resulted in a change in the landscape of diagnosis and investigation of the modalities of disease, particularly in the dementias, including Alzheimer's disease (AD), Lewy body disease, and frontotemporal dementia, beginning in the early 1900s. Chronic diseases have become the primary causes of not only mortality, but also morbidity. This applies for HICs, as well as for LMICs where this process is under way.

With the shift in world age demographics, the population that will experience the greatest increase in risk of disease and disability will no longer be infants, but individuals aged 60 years and older. Both HICs and

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LMICs will therefore have to face the challenge of increases in chronic disorders, especially those disorders that are prevalent in the older aged population. This raises issues regarding prevention and treatment, as behavioural and genetic risk factors are a hallmark of this era; preventive measures are less effective, and treatments are more complex and can be lifelong, and therefore expensive.

Basic epidemiologic measures

(See Box 4.1.)

Box 4.1 Basic epidemiological concepts

- Prevalence:
$$\frac{\text{Number of cases in a population at a given period of time}}{\text{Population at the same given time}}$$
- Incidence:
 - Cumulative incidence:
$$\frac{\text{Number of new cases in a population at a given period of time}}{\text{Number of individuals at risk of developing the condition at the same given time}}$$
 - Incidence density rate:
$$\frac{\text{Number of new cases in a population at a given period of time}}{\text{Sum of the follow-up times for each individual at risk of developing the condition}}$$
- Lifetime risk:
 - Probability of someone of a given age and sex developing a condition during their remaining lifespan
- Disability-adjusted life years (DALYs):
 - Years of life lost due to premature mortality + years lost due to disability for incident cases

Prevalence

The prevalence of a condition in a population is defined as the total number of cases over the number of individuals in a population at a given time. It indicates how widespread the condition is, and it may be regarded as a snapshot of the number of affected cases in a population.

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Prevalence is determined by the duration of a disease and the quantity of new cases. It is important for developing management and health service planning, as well as eradication programmes. As prevalence is measured at a given time, it is used to reveal cross-sectional associations with other variables. Such cross-sectional associations do not account for the temporal sequences of events and therefore cannot be used to establish causation. Furthermore, in neuropsychiatric syndromes, the prevalence figure is greatly influenced by operational and disease diagnostic/classification criteria.

Incidence

Incidence relates to new cases; it is a measure of the risk of developing a new condition within a specified period of time. The incidence rate is expressed either as a cumulative incidence with the number of new cases over some period of time, but also it can be expressed as a density rate when the denominator is the sum of the person-time of the at-risk population. The latter is a more precise estimate of the rate of occurrence of a particular disease, especially in cohort studies where the length of time that participants stay in the study varies. The density rate contrasts the number of new cases with the sum of the time that each person remained under observation and free from disease.

As incidence studies are more expensive and time-consuming, most of our knowledge about the epidemiology of neuropsychiatric conditions is based on prevalence, rather than incidence, studies.

Incidence can be used to determine the impact of management and treatment strategies, to identify risk factors and natural history, and to appropriately allocate future resources (e.g. public health initiatives, prevention and intervention strategies and funding for research). It is measured from data obtained in cohort studies; therefore, the temporal sequence of events is captured, allowing for the inference of not only associations, but also causation. However, estimates may be influenced by unexpected changes in the environment and the population tested (e.g. population-specific differences in risk and protective factors) and can be affected by difficulties in certainty of distinguishing new and old cases. The collection of data needed to calculate prevalence and incidence can be challenging and costly. Incidence is difficult to define in neuropsychiatric conditions, as these diagnoses are based on clusters of symptoms that vary in severity and fluctuate over time. Further, neuropsychiatric conditions are highly comorbid, with symptoms being shared by multiple diagnoses.

Lifetime risk

The definition of lifetime risk of a condition is the probability that a person who is currently free of the condition will develop it at some time during the remainder of their expected lifespan (Seshadri and Wolf, 2007). The lifetime risk of a disease is the risk over a long period, rather than the risk over a year, which is the age-specific annual incidence of the

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disease (Seshadri and Wolf, 2007). Operationally, the lifetime risk is the conditional probability of developing a disease when a person has reached the index age and is free of that disease. Its estimation enables a long-term perspective, which is especially useful for chronic conditions such as dementias where exposure to risk factors in mid-life can alter the incidence of disease in later life.

Disability-adjusted life years

The concept of disability-adjusted life years (DALYs) was designed to measure the global burden of a disease. It has the advantage of aggregating mortality and morbidity in a single tool. Consequently, it allows the evaluation of burden of diseases with low mortality. The DALY corresponds to the time lived with disability and the time lost due to premature mortality. This methodology uses epidemiological data and vital statistics, which are normally available even in LMICs, facilitating international comparisons and evaluations of the impact of international investments and health policies (Murray, 1994).

DALY is calculated as the sum of the years of life lost (YLL) due to premature mortality in the population and the years lost due to disability (YLD) for incident cases of the health condition:

$$\text{DALY} = \text{YLL} + \text{YLD}$$

The YLL is calculated from the number of deaths multiplied by the standard life expectancy at the age at which death occurs, which is derived from the model life-table West Level 26 which has a life expectancy at birth of 82.5 years for females and 80.0 years for males. The basic formula for YLL for a given cause, age, and sex is:

$$\text{YLL} = \text{number of deaths} \times \text{standard life expectancy at age of death in years}$$

To estimate YLD for a particular cause in a particular time period, the number of incident cases in that period is multiplied by the average duration of the disease and a weight factor that reflects the severity of the disease on a scale from 0 (perfect health) to 1 (dead):

$$\text{YLD} = \text{number of incident cases} \times \text{disability weight} \times \text{average duration of the case until remission or death (years)}$$

Additionally, 3% time-discounting and non-uniform age weights which give less weight to years lived at young and older ages might be incorporated into the calculation of DALYs. Unequal age weights are an attempt to capture different social roles at different ages. The young, and often older individuals too, depend on the rest of society for physical, emotional, and financial support. Given different roles and changing levels of dependency with age, it may be appropriate to consider valuing the time lived at a particular age unequally (Murray, 1994).

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The epidemiology of neuropsychiatric disorders

Neuropsychology aims to better understand the relationship between the brain and behaviour. This section will explore the epidemiology of neuropsychiatric conditions in ageing populations, with a focus on the dementias and depression, including their diagnosis, prevalence, incidence, and risk factors (where available). Evidence will be gathered from longitudinal population-based studies that have included a focus on ageing from across the world.

The global burden of old age neuropsychiatric conditions

Disability-adjusted life years

From a psychiatric point of view, recent estimates generated by the Institute of Health Metrics and Evaluation Global Burden of Disease 2010 suggest that neurological and mental disorders contribute to 6.6% of the total DALYs of the global population aged 60 years and older (Prince et al., 2015). More specifically, dementia accounted for 10.0 million DALYs in people aged 60 years and older, with 44% of the burden arising in LMICs. This figure is behind the contribution of ischaemic heart disease (77.7 million), cerebrovascular disease (66.4 million), chronic obstructive pulmonary disease (43.3 million), and diabetes mellitus (22.6 million).

Mortality of dementia

Guehne et al. (2005) conducted a review study of the mortality risk in dementia and potential influencing factors, based on population-based samples. They found that, apart from the methodological differences between longitudinal population-based studies, which this chapter will later cover intensively, all types of dementia, without exception, were associated with a considerably increased mortality risk. Moreover, the risk of death rises with advancing severity of the disorder. The authors recommended the use of incident dementia cases to calculate the course of dementia and the mean survival time more precisely. For incident cases of dementia, the time of onset of the disorder could be assumed to be the midpoint between the baseline and follow-up interview or date of death, provided that follow-ups were conducted at short intervals. However, only few studies have based their findings on incident cases. Aguero-Torres et al. (1999) calculated a mean survival time of 3.0 years among individuals aged 75 years and older with incident dementia, in contrast to a mean survival time of 4.2 years for persons without dementia. Helmer et al. (2001) reported a mean survival time in incident cases of 4.5 years among 65-year olds and a relative risk of 1.8 [95% confidence interval (CI) = 1.8–2.7]. Xie et al. (2008) observed a median survival time of 4.1 years (interquartile range 2.5–7.6) for men and 4.6 years (interquartile range 2.9–7.0) for women. Regarding the influence of education and occupation, some studies have found individuals with dementia and lower education having a *higher* survival time (Helmer et al., 2001; Qiu et al., 2001). A shorter survival time for highly educated individuals with dementia could

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be explained by their ability to continue living an independent life for longer, resulting in late recognition of the disease. It is presumed that there is a similarly fast progression of the underlying pathological processes, which means that, because of later recognition, highly educated persons may live with this condition for a shorter period of time and therefore present an apparently higher mortality rate (Guehne et al., 2005).

Mortality of depression

There is a well-established risk of suicide among individuals with depression and this risk is recognized not only among younger patients suffering from depression, but also among older people as well. However, depression, specially in older people, can be a consequence of medical illness and disability, and it may also influence morbidity and mortality through a variety of behavioural and biological mediators (Schulz et al., 2002). A systematic review examining the relationship between depression and non-suicidal mortality reported that there is evidence supporting an association between the two and the mechanisms that might account for this relationship (Schulz et al., 2002). The review found that rates of mortality were higher in studies: (1) with larger sample sizes; (2) where depression was assessed by a structured diagnostic interview, rather than a psychiatric examination (and, in turn, these were both higher than self-report measures); and (3) in matched control groups, compared to cohorts (and both more than general population studies). Of the studies that were restricted entirely to late-life population samples, ten (67%) disclosed positive reports and five (33%) negative reports. Among those positive studies, the relative risks for depression as a predictor of mortality varied from 1.2 to 4.0, with the majority of studies falling in the 1.5–2.5 range. Depression might increase the likelihood of dying through several factors such as poor adherence to treatment of comorbidities, poor maintenance of cognitive and physical function, and withdrawal from social networks.

Methodology

Prevalence and incidence are heavily influenced by study design, methodological differences, population uptake, and cultural factors (Brayne, 1993). This has hampered worldwide comparisons. However, there are strong examples of standardized methods across combined studies such as used in the 10/66 study discussed later in this chapter.

Case definition

To study disease incidence, prevalence, duration, and severity, the definition of what is a case is important. For some conditions, such as most infectious and parasitic diseases, this is a straightforward process. By isolating the aetiological agent or antibodies against the agent, the presence of disease can be determined. In some individuals, this may manifest in clinical symptoms, while in others it may not. However, with neuropsychiatric disorders, the diagnostic process is more involved, given

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each classification is based on a combination of symptoms and their quantity, duration, and intensity, and the fact that these symptoms vary across a spectrum in the population. There is therefore more difficulty in conceptualizing what a mental disorder is and in determining whether it is present or not. This is particularly difficult among the older population since medical comorbidity is common and may affect symptom profiles and interfere with functioning through, for example, polypharmacy or disease-related effects on mood and other mental functions.

Cultural aspects

Cultural concepts of diseases may lead to different expectations of what is considered mentally normal. World views towards ageing vary immensely, and as a consequence, cultural concepts influence the awareness of diseases, especially mental disorders, and the utilization of services. Furthermore, the application of standardized diagnostic instruments may not always be culturally appropriate.

In the clinical setting, patients or carers have to perceive a symptom as an abnormal feature to seek help and for the person to be defined as a case. In contrast, in most epidemiological studies, a case is defined by means of structured questionnaires in which responses will be balanced to check against a set of operational criteria; therefore, this does not rely solely on an informant's opinion, but also on informant standardized information, which, in essence, can minimize cultural bias.

There have been examples over time of studies examining indigenous and migrant populations. In a study of Cree Indians living on two reserves in Manitoba (Canada), the age-adjusted prevalence of dementia was equivalent to whites living in Winnipeg (4.2% for both groups), but AD prevalence was lower (0.5% versus 3.5% in whites) (Hendrie et al., 1993). In the UK, vascular dementia has been found to be more prevalent than AD in individuals of African Caribbean origin (versus British Caucasians) (Livingston et al., 2001; Richards et al., 2000). Paraiso et al. (2011) found that dementia in an urban area of Benin (West Africa) (3.7%; 95% CI 2.6–4.8) was slightly higher than the figure obtained in the city of Ibadan (Nigeria) of 2.3% (95% CI 1.7–2.9), but the rate was similar to that recorded in other cities in LMICs, including India (Kocki, Kerala) and countries in Latin America.

There are a number of factors which could explain the difference in prevalence estimates for dementia across different populations. First are methodological differences (i.e. in the screening tests used, the diagnostic criteria applied, sampling, etc.). Second are genetic factors and variations in risk genes across populations that could lead to differences in prevalence. Third, symptoms have to be perceived as an abnormal feature. Variations in the environment, including education and social meaning of cognitive changes with ageing, all influence how soon individuals seek medical help. Last are issues around cognitive testing which is typically biased towards those with higher levels of formal

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education, and therefore, those without may be directed towards a diagnosis of dementia when, in fact, the instrument was not culturally relevant to them. There have been a number of attempts to overcome this limitation such as the development of the Kimberley Indigenous Cognitive Assessment (KICA) for use with indigenous Australian populations. This is a modification of the Mini-Mental State Examination (MMSE) and asks culturally relevant questions/knowledge.

In a study of reflections of the onset and diagnosis of dementia among African American, Chinese, and Latino family caregivers in the United States, minority ethnic groups were found to convey striking cross-cultural similarities in the characterization of initial memory changes as normal ageing (Mahoney et al., 2005). As dementia symptoms progressed, however, cultural differences emerged. Normalization of cognitive symptoms until the precipitation of one critical event appeared to be most prolonged among African Americans; Chinese subjects seemed to be the most concerned about stigmatization.

Diagnostic methods

Numerous attempts have been made to deal systematically with the concepts and methods of assessment in neuropsychiatry. However, depending on the system of diagnostic classification used for a case definition, an individual can be identified as being a case according to one system, but not a case according to another. For most neuropsychiatric disorders, different diagnostic classification systems include different combinations of symptoms which reflect impairments in cognitive, emotional, and social abilities to inform the process of diagnosis. Furthermore, there is the issue of changes in diagnostic criteria over time [i.e. third (DSM-III) versus fifth (DSM-5) edition of the *Diagnostic and Statistical Manual of Mental Disorders*]. Therefore, the use of different criteria jeopardizes comparisons between studies, as they may classify the participants differently (e.g. diseased versus not diseased) (Erkinjuntti et al., 1997).

Erkinjuntti et al. (1997) examined the effects of six commonly used classification schemes on the prevalence of dementia in a population-based cohort of older people. The classification schemes used were the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) (American Psychiatric Association, 1980), the DSM-III-R (American Psychiatric Association, 1987), the DSM-IV (American Psychiatric Association, 1994), the ninth edition of the International Classification of Diseases (ICD-9) (World Health Organization, 1977), the ICD-10 (World Health Organization, 1992), and the Cambridge Mental Disorders of the Older Population Examination (CAMDEX) (Roth et al., 1986). They found that although there was substantial overlap among the groups of persons identified by the various systems, the frequency of dementia varied, depending on the scheme used. The frequency of dementia was 3.1% using the ICD-10, 4.9% with CAMDEX, 5.0% with ICD-9, 13.7% with DSM-IV, 17.3% with DSM-III-R, 20.9% according to the

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Canadian Study of Health and Aging (CSHA) clinical-consensus method (Canadian Study of Health and Aging Working Group, 1994), and 29.1% with the DSM-III criteria. However, while dementia prevalence varied, depending on the diagnostic criteria used, the frequency of dementia increased with increasing age for each classification method.

The ICD has existed for more than a century; it is global, multidisciplinary, and multilingual and is ratified by all 193 World Health Organization (WHO) member countries. On the other hand, the DSM was developed by the American Psychiatric Association, focuses specifically on mental disorders, and does not have such an international approach. As diagnosis in psychiatry is mostly descriptive and based on a collection of symptoms, the ICD and DSM diagnostic classifications are functionally equivalent in clinical settings. However, in epidemiological studies where structured interviews are usually employed, such differences become more important (Andrews et al., 1999).

Another methodological issue regarding the diagnosis of dementia or its subtypes is that diagnostic criteria have changed over the years, as new investigations became available. To illustrate this, the diagnosis of probable dementia with Lewy bodies (DLB) was initially based solely on clinical criteria such as the presence of dementia, visual hallucinations, fluctuations, and parkinsonism (McKeith et al., 1996). However, the third report of the Consortium on DLB International Workshop (McKeith et al., 2005) included dopamine transporter imaging among the diagnostic criteria. This technique is a functional imaging of the dopamine transporter and defines the integrity of the nigrostriatal dopaminergic system. Regarding neuropathological criteria, originally the only requirement for DLB was the presence of Lewy bodies somewhere in the brain of a patient with a clinical history of dementia. In contrast, the new criteria take into account the extent of Lewy body-related pathology and AD-type pathology in assessing the degree of certainty that the neuropathological findings explain the DLB clinical syndrome. Moreover, the use of new immunohistochemical staining techniques, such as α -synuclein which replaced the former ubiquitin immunohistochemistry for identifying α -synuclein, has been shown to be a more sensitive and specific method for detecting Lewy bodies.

Diagnostic criteria for vascular dementia and AD have also changed as a result of updates in scientific knowledge and technological advances. For AD, in the last 8 years, new guidelines, i.e. the National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria released in 2011, as well as revisions of major diagnostic criteria have been released, including updates to the American Psychiatric Association's DSM-5, released in 2013; and WHO's ICD-11, released in 2018 (Stephan et al., 2014). The key aims have been to improve diagnosis in clinical/research settings, including: (1) identifying underlying causes; (2) capturing different diagnostic thresholds (e.g. prodromal, preclinical, and earlier clinical states such as mild cognitive impairment (MCI) and mild neurocognitive disorder); (3) reducing stigma; and (4) enhancing

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research. A part of the research criteria proposed by the NIA-AA guidelines was the introduction of biomarkers into diagnosis, including determination of brain amyloid-beta ($A\beta$) accumulation [e.g. low cerebrospinal fluid (CSF) $A\beta_{42}$ level and positive PET amyloid imaging] and neurodegeneration (e.g. MRI/PET evidence of whole brain/hippocampal atrophy, functional impairment identified using ^{18}F -fluorodeoxyglucose PET or functional MRI, and tau levels as indicated by CSF). As new promising biomarkers become available (e.g. blood-based biomarkers), it is likely that these will be introduced into updated diagnostic criteria.

For vascular dementia, in the early nineties, Roman et al. (1993) emphasized the importance of brain imaging to support clinical findings for vascular dementia. The term vascular cognitive impairment (VCI) has also been proposed that broadly encompasses cognitive deficits associated with vascular disease and its risk factors ranging in severity from mild to vascular dementia or mixed vascular dementia where cerebrovascular and AD pathologies co-occur (Harrison et al., 2016; Skrobot et al., 2018). In the updated edition of the American Psychiatric Association's DSM-5 (released in 2013), under the term 'Major Neurocognitive Disorder: NCD' are steps to assign aetiological categories to dementia such as Alzheimer's NCD or vascular NCD. Differentiation is based on clinical criteria that can be operationalized, including additional diagnostic markers such as neuroimaging (i.e. MRI/PET) and other biomarkers.

This instrumentalization of medicine impacts on epidemiology, as medical diagnosis theoretically becomes more accurate and effective, but at the same time these technologies might label individuals as diseased without them having experienced any symptoms at all and without knowing if they will ever present symptoms of the given disease. From an epidemiological perspective, the critical fact here is how these newly suggested criteria perform in samples representative of the general population. It is important to highlight that although dementia is considered a progressive disorder, in population settings, the course of symptomatology is hugely variable.

Classification problems also emerge when attempts to define the transitional state between 'normal' ageing, pathological decline, and progression into dementia are made. Although several classification systems claim to represent this intermediate stage, most prominently MCI, their criteria, and therefore outcomes, differ. To illustrate this, Matthews et al. (2008) compared the 2-year outcome of 16 different classifications in the same population-based setting. They found that the overall progression was highest in classifications in which impairment extended to memory and non-memory domains such as multiple domain mild cognitive impairment (m-MCI) (14.3%), mild neurocognitive disorder (MNCD) (31%), and mild cognitive disorder (MCD) (29%). On the other hand, the conversion rate for age-consistent memory impairment (ACMI) was 0.3% and for age-related cognitive decline (ARCD) 4%, showing that

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these classifications captured lower-risk groups in the population with greater stability and reversion to normality.

In many clinical research centres, the diagnosis of dementia is made based on a consensus approach, which relies on a multidisciplinary panel of expert clinicians who meet to review detailed information on various aspects of a given person such as clinical examination and informant reports of cognition, behaviour, functional impairment, and neuropsychological diagnosis. This process allows each study participant to be individually considered in detail (Weir et al., 2011). However, in such cases, the diagnosis process is inevitably influenced by the clinicians' philosophy, personality, discipline, culture, and inherent biases. Although clinical examination is of extreme importance, in the context of epidemiological research, to ensure cross-study comparisons, it is crucial to standardize the process of data collection such as cognitive function, activities of daily living, physical health, and behavioural and psychological symptoms of dementia. Otherwise, study validity might be jeopardized by between-clinician variability and changes in diagnostic criteria over time (Brayne et al., 2011).

In the context of psychiatric studies, the Present State Examination was developed as a standardized instrument (Wing et al., 1967). This instrument was adapted by Copeland et al. (1976) and renamed the Geriatric Mental State (GMS) Examination, which was designed to detect dementia, depression, and other mental illnesses in the older aged population by generating diagnostic algorithms (Copeland et al., 1986), validated against the clinical diagnostic process based on the DSM-III-R. The aim was to introduce a more structured approach to diagnosis that could be used by non-clinicians. Unlike clinicians who quickly narrow down to the presenting diagnosis, structured interviews systematically explore each diagnostic criterion before assigning a diagnosis. Studies with a large number of participants make a quasi clinical diagnosis possible by adopting this diagnostic algorithm, based on the assumption that interviewers are trained to administer questions or conduct examinations in a standardized manner (Brayne et al., 2011). Recently, there has been renewed interest in the algorithm approach (Weir et al., 2011).

Interviews

Data collection can be made by means of a written questionnaire, telephone interview, face-to-face interview with participants or their informants, or even extraction from case records and death certificates. Semi-structured interviews are preferred when there is the need to gather qualitative data, whereas in structured interviews, standardization is easily obtained to the detriment of qualitative information. In structured interviews, there is a tightly scripted text from which the interviewers are not supposed to deviate. Examples of highly structured interviews are the CAMDEX (Roth et al., 1986) and the Geriatric Mental State Examination/Automated Geriatric Examination Computer Assisted

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Taxonomy (GMS/AGECAT). The neurological examination in the CAMDEX is more comprehensive than the GMS. The 10/66 study, which demands high standardization due to cross-country data collection, has used two approaches for dementia diagnosis—one based on the GMS/AGECAT and the other based directly on the DSM-IV criteria.

Interviewers

In large-scale surveys, there is a tendency to recruit non-clinical interviewers to collect the data, provided the interview is structured. Naïve trained interviewers are known to be very adept at administering structured interviews in a consistent manner. Depending on what is included in the assessment protocol, there may still be a need for qualified professionals. For example, if a physical examination is intended, a doctor would normally be required (Butler and Brayne, 1998). In some multi-stage studies, lay interviewers are used in the first stage and medical doctors in subsequent stages, as in the ALPHA Liverpool study (Saunders et al., 1993) and the Nakayama study (Ikeda et al., 2001). In the Soham study, a clinician administered the CAMDEX to all participants (Brayne et al., 1997).

Sampling

To define the sampling frame of a study, the site of the study has to be defined, as well as the sample procedure. The study site might be defined geographically or, for example, be composed of individuals registered in a specific organization, such as a primary care trust, hospitals, a health care system, a retirement community, or a nursing home, or participants of an electoral register. The sample procedure might include the entire population above a certain age or use a sampling strategy to select a representative subgroup of manageable size such as random selection or systematic selection. Furthermore, stratification according to age groups, sex, or other variables (e.g. ethnicity) can also be used to not over-represent groups.

Population and community-based studies

Few studies are truly representative of the whole population. Many others would be more accurately described as population-derived, e.g. many exclude individuals in institutions. These are studies where a general population defined by geographical boundaries is the sampling frame (Poels and Last, 2008). It is well known that referral of patients can cause population bias, affecting the results of epidemiological studies (Sackett, 1979). According to the Goldberg-Huxley model of the pathway from the community to the hospital in terms of psychiatric care, there are five levels and four filters (Goldberg and Huxley, 1980). People with severe illnesses pass more easily through the filters to secondary professional care than do people with common mental disorders.

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Not only is referral influenced by the condition itself, but it may also vary according to burden of symptoms, family recognition of a problem, access to health care, popularity of the condition, and the presence of specialized centres nearby (Brayne, 1993). Furthermore, specialized patient research groups derived from referrals typically use stringent selection criteria, so that patients are usually selected to have fewer comorbid conditions. As an example, the occurrence of behavioural symptoms among patients with dementia is often the triggering event for recognition and referral to health care, rather than the cognitive impairment itself (Lawlor, 2002). It is therefore important to differentiate between population-based studies and community-based studies. Where the first are potentially of use when generalizing the findings to the whole population, the latter often are restricted to members of a selected community which does not necessarily represent the population. An example is the Nun study where the entire community of nuns was involved in a longitudinal study (Snowdon et al., 1996). However, it is likely that this religious community is very different from any general population sample, and therefore, the nature of risk exposure and outcome may be different from the general population. However, depending on the research question, some findings might be suitable for generalizing purposes.

Another point that should be highlighted is that some studies may exclude individuals who live in institutions. Many countries do not have the possibility of sampling from both general and institutionalized populations. This may lead to underestimation of the prevalence and, in longitudinal terms, underestimation of decline or mortality. Larson et al. (2004) reported findings from a survival study on community-dwelling patients with AD (Larson et al., 2004) where men had a median survival of 4.2 years from their initial diagnosis and women had a median survival of 5.7 years. These estimates were longer than the ones of the Canadian Study of Aging (Wolfson et al., 2001) where the median survival was 3.2 years for men and 3.4 years for women. These differences are likely due to the Canadian Study of Aging including nursing home residents who were at a later stage of disease.

Stratification

Some epidemiological studies of dementia have used more than one-stage diagnostic procedures to optimize resources. In the first stage, a brief and inexpensive screening instrument (such as the MMSE) is administered, followed by more complex, time-consuming, and expensive tests in the second stage. Typically, all those people who screen positive (e.g. below a cut-off score on the MMSE), along with a random sample of the remainder, are seen again using more comprehensive diagnostic tools, which usually include a structured clinical assessment, a more extensive multi-domain test of cognitive function, and a structured interview with an informant. The second-stage assessment may also include a physical examination, a brain scan, and a collection of biological samples. Although a multi-stage design makes diagnostic procedures more efficient, it carries a serious problem of refusal or non-availability.

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Furthermore, it is more prone to bias due to incorrect analysis of partially verified data where screened-negative participants who were not selected for the second stage are considered as true negatives or are simply excluded from the analysis. As a consequence, sensitivity and specificity are poorly estimated (Yu and Zhou, 2012). Other studies, to overcome these biases, randomly select the participants for the second stage, weighting towards cognitively impaired persons to allow for inferring the sample results back to the whole population (for example, The Medical Research Council Cognitive Function and Ageing Study (MRC CFAS), 1998). But the analyses are rarely indicated with full attention to the multiple stages and rates of dropout (Matthews, 2005). This over-inflates power in that the reported confidence intervals are, in fact, too narrow.

Screening tool: a focus on the MMSE

The MMSE is one of the most widely applied tools in clinical and research practice to screen for cognitive impairment and dementia. However, there are disagreements regarding the best cut-off score to distinguish impaired versus not impaired (e.g. 18, 21, 22, 24, or 26) and whether cut-off scores should be adjusted for age and education levels. In high-functioning samples, the MMSE is found to suffer from ceiling effects, and in low-functioning samples from floor effects. Both extended, such as the extended mental state examination (Huppert et al., 2005), and abbreviated versions, such as the 11-item version used in the European Prospective Investigation into Cancer (EPIC-Norfolk) (Matthews et al., 2011) have been created to overcome these issues. Further, due to copyright law restrictions, new brief and free screening tests that also measure cognitive function, such as the Sweet-16 (Fong et al., 2011), are becoming available and are likely to become more widely used.

Influence of other variables

Performance on cognitive tests may be influenced by many factors other than cognitive impairment such as educational background, cultural experiences, prior testing experience, emotional and physical states, the testing environment, use of medicines, and measurement error. This makes it difficult to control and compare such measurements in different studies, even if the same tool is used to assess cognition. Furthermore, most tests currently used are subject to ceiling and floor effects (Morris et al., 1999; The Medical Research Council Cognitive Function and Ageing Study (MRC CFAS), 1998).

Missing data

Almost all studies have some missing observations. Missing data can arise due to non-response at baseline, death, or dropout from the study, as well as item non-response. Longitudinal and multi-stage studies are especially prone to be subject to missing data due to death or dropout. The main concern is that in those cases, missing data are not at random and do affect final estimations. Participants with cognitive impairment are more

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likely to drop out from a study than healthy individuals. Chatfield et al. (2005) performed a systematic review to investigate large population-based studies of older individuals that reported on attrition between waves of a follow-up in a systematic manner. The review concentrated on dropout due to refusal, sickness, inability to locate individuals, or individuals moving away from a defined study area. They found that increasing age and cognitive impairment were the two main independent factors related to increased attrition. People who were very ill or frail had higher dropout rates, and people in worse health were less likely to be contactable on a second occasion. As these factors are not preventable, the authors suggested that over-sampling of these groups in the initial phases could be used to ensure that sufficient numbers of participants remain at follow-up. Also, the follow-up methods can be adjusted to ensure maximum participation in those individuals with cognitive impairment. The length of the interview can be modified, and a proxy interview can be used in a wider range of situations (Chatfield et al., 2005). Saxton et al. (2009) compared rates of MCI and rates of progression to dementia using different MCI diagnostic systems, and regarding dropouts, they found that MCI status at baseline was significantly associated with dropouts lost to follow-up. Obviously, loss of participants also reduces the power of a study.

Missing data are even more common in retrospective studies, in which routinely collected data are subsequently used for a different purpose. When information is gathered from participants' medical records, the notes often do not point whether or not a participant has the required risk factor. It is unwise to assume that the answer is not present when there is no indication that the risk factor was sought (Altman and Bland, 2007). There is no really satisfactory solution to the problem of missing data. The main ways of handling missing data in analysis are omitting variables or individuals who do not have complete data, or imputation whereby missing values are estimated from that individual's available data (Altman and Bland, 2007). Ignoring missing data in the analysis is a common approach; however, it might bias the results as data are rarely missing at random in cohort studies. Although imperfect, multiple imputation is recommended for handling missing data. Such models not only can control for the fact that dropout has occurred, but also, where available, may include information on the reason for dropout. Following imputation, sensitivity analysis can be run to check for similarity in observed associations in the restricted (e.g. complete-case analysis), compared to the imputation-derived, data set.

Age, period, and cohort effects

Age, period, and cohort effects are closely interrelated, as age is the result of a given year (period) minus the year of birth (cohort). Szklo and Nieto (2007) proposed a definition of age, period, and cohort effects where age effect is the change in the rate of a condition according to age, irrespective of birth cohort and calendar time; cohort effect is the change in the rate of a condition according to year of birth, irrespective of age

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and calendar time; and period effect is the change in the rate of a condition affecting an entire population at some point in time, irrespective of age and birth cohort. To better understand the definition of age and cohort effects, it is easier to approach them by fixing one parameter.

Age effect—let us suppose that the prevalence of a condition was measured in a single group of people born in the same year (single birth cohort) in wave-1. Five years later, the prevalence of the same condition was measured again (wave-2), and 10 years later (wave-3) in the same original group of people. If the prevalence of this condition changes between waves, this is a representation of an age effect.

Cohort effect—this can be obtained when a study is interested in looking at the prevalence of a condition only at a given age (let us say 60 years) and does so by recruiting 60-year-old individuals in wave-1, a different group of 60-year-old individuals in wave-2, and a third 60-year-old group in wave-3. If the prevalence of this condition changes between waves, this is a representation of a cohort effect, as, in fact, the different birth cohorts were compared longitudinally. The cohort effect can be seen as a result of the risk factors and environmental exposures that are present in early life or are typical for a given generation.

Period effects—these are the consequences of any phenomenon occurring at a specific point in time, which affects the entire population, reflecting changes in prevalence of a given condition across all age groups and birth cohorts (Szklo and Nieto, 2007). This is the case with wars, new curative treatments, vaccines, etc.

Regarding dementia, age effects are well established across studies, but cohort effects have historically been controversial. In the Lundby study, from 1947–1972 to 1972–1997, a decrease in the incidence of dementia was found in all age groups, except in the 40–49 interval (Bogren et al., 2007). Whether or not it is a true cohort effect or an artefact is not known. On the other hand, Rocca et al. (2011) analysed data from four studies to verify if declines in age-specific prevalence and incidence rates for dementia have occurred in recent years. Three of those were community-based studies—one conducted in Rochester, Minnesota (1975–1994) (Knopman et al., 2006); the Indianapolis branch from the Indianapolis-Ibadan Dementia Project (1992–2001) (Hendrie et al., 1995), the Chicago Health and Aging Project (1997–2008) (Hebert et al., 2010)—and a national survey the Health and Retirement Study (<http://hrsonline.isr.umich.edu>) (Juster and Suzman, 1995). In the Minnesota cohort, there were no differences in incidence across the ten birth cohorts, but a marginal decline for dementia was observed. The Chicago Health and Aging Project did not find a relationship between the calendar year of evaluation and disease incidence, which suggests no change in incidence over time. In the Indianapolis-Ibadan Dementia Project, although they found that the 2001 cohort had higher levels of hypertension, diabetes, and stroke, there were no differences in the

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prevalence of dementia. The Health and Retirement Study did not assess dementia directly, but 'cognitive impairment consistent with dementia' (CI-D) based on a 35-point cognitive scale or proxy's assessment of the respondent's memory for those who were not self-respondents. The authors reported that the prevalence of CI-D had an absolute decrease of 3.5 percentage points and a relative decrease of nearly 30.0%. Furthermore, the prevalence of some cardiovascular risk factors increased significantly, but higher levels of education were found in the most recent cohort.

The ZARADEMP project (Lobo et al., 2007) investigated possible cohort effects regarding the prevalence of dementia in Zaragoza, Spain for 1988 versus 1994. The authors found that there was stability in the global prevalence of dementia over time, but a decrease among men aged between 70 and 84 years. It is interesting to note that the prevalence of dementia in men found in the first cohort was also higher than in European pooled data reported during the EURODEM Concerted Action study (Lobo et al., 2000). Although in ZARADEMP, the two time points were probably too close together to detect differences in environmental exposure, the authors pointed out that the Instituto Nacional de Estadística had reported improved control of potential risk factors for dementia, such as smoking habits, diabetes, and cardiovascular disorders, in Spain.

More recent studies, summarized in three reviews (Prince et al., 2016; Stephan et al., 2018; Wu et al., 2017), suggest that in some (but not all) regions, an individual's risk of dementia may be declining or remaining stable, including, for example, studies from the UK (Matthews et al., 2013 and 2016), the United States (Satizabal et al., 2016), and France (Grasset et al., 2016). The evidence also suggests that in South East Asia, the risk of dementia is increasing—a result possibly linked to changes in health status (i.e. increases in the number of individuals with cardio-metabolic disease), lifestyle patterns (i.e. changes in dietary habits and reduced physical activity levels), and/or dementia awareness (including changes in diagnostic criteria).

Despite methodological challenges, considerable attempts have been made to compare and combine findings from epidemiological studies that focus on the most common and debilitating neuropsychiatric disorders in old age psychiatry, including dementia and depression. These studies will be presented in this chapter.

Importance of neuropathological studies in the epidemiology of dementia and its subtypes

'Plaques' in the cerebral grey matter were first described by Blocq and Marinesco in 1892 and related to the pathology of senile dementia by Simchowicz who named them as 'senile plaques' (Blessed et al., 1968). In 1907, the neuropathological findings of neurofibrillary tangles in degenerated neurons and senile plaques deposited in the cortex were

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first linked to a presenile dementia syndrome (Alzheimer et al., 1995). At first, this combination of presenile dementia, neurofibrillary tangles, and senile plaques, described by Alois Alzheimer, was thought to be a rare disease, separated as a distinct entity from senile dementia and was baptised as AD (Berrios, 1990; Zilka and Novak, 2006). These ancient reports were based on case reports and small groups of patients.

It was not until 1966 that an investigation of the nature and extent of the relationship between plaque formation and mental deterioration in old age was undertaken in a clinic-based study (Roth et al., 1966) conducted on patients admitted to a psychiatric hospital, a geriatric hospital, and several wards in a general hospital. The severity of dementia in individuals during life was ascertained to determine whether this bore any relationship with mean plaque counts in the cerebral grey matter. These assessments were repeated at 6-monthly intervals on survivors. Roth et al. concluded from the results of 37 patients that, far from being irrelevant to the pathology of old age mental disorder, the density of plaque formation in the brain highly correlated with quantitative measures of intellectual functioning. When the sample was expanded to 60 patients, the results were consistent, showing a highly significant correlation between mean plaque counts and scores for dementia and performance on psychological tests (Blessed et al., 1968). The plaques seen in authenticated cases of AD were indistinguishable on light microscopy from those investigated in their study. This observation led to the realization that half or more cases of senile dementia were associated with the same neuropathology that characterized the early-onset dementia of AD.

Significant knowledge of the clinical features and neuropathology of the different types of dementia has come from observations on the brains of individuals with dementia from nursing homes, acute medical units, hospitals, or ordinary post-mortem series (Zaccai et al., 2006). However, the nature of these services can lead to selection bias which influences the findings of the studies. Schneider et al. (2009) investigated the differences in neuropathological findings from persons with and without dementia in clinical versus community-based settings. They compared the neuropathology underlying no cognitive impairment, MCI, and dementia from two community-based cohorts and one clinic-based cohort. They found that community-based participants with probable AD showed less severe AD pathology and more often had infarcts and mixed pathologies, while those with MCI more often had infarcts and mixed pathologies. Also, clinic-based individuals had more Lewy bodies and atypical pathologies. Based on these results, the authors concluded that the spectrum of pathologies underlying cognitive impairment in clinic-based cohorts differs from community-based cohorts (Schneider et al., 2009). For extrapolation of results to the population to be valid, research must be conducted on a true population sample or on groups with well-characterized biases.

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As dementia is a chronic and progressive disorder, it is impossible to determine the exact point when an individual developed dementia. In addition to uncertainty regarding symptom onset is a lack of certainty in diagnosis. In inter-observer studies, the clinical diagnosis of AD is not 100% correct in all cases (Holmes et al., 1999; Richards and Brayne, 2010; Scheltens and Rockwood, 2011; Xuereb et al., 2000). Some classification criteria, such as the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA), rely on histopathological confirmation to diagnose AD as a definite condition (McKhann et al., 1984). As a consequence, AD is therefore framed as a neuropathological entity in spite of the fact that the diagnosis of AD in living patients is made on the basis of clinical information (Richards and Brayne, 2010). In contrast, dementia is a syndrome, rather than a neuropathological diagnosis (Xuereb et al., 2000), and so a clinical diagnosis of AD assumes dominance of Alzheimer pathology as the cause of dementia in those patients.

The pathological criteria for AD were derived from brains originally from a highly selective clinical sample. However, the brains of people included in truly population-based neuropathological studies of dementia have a high percentage of mixed pathologies, which challenges the pathology-led model of diagnosing definitive AD. The first study to disclose such a pattern in a systematic way reported on autopsied brains of 101 participants (Xuereb et al., 2000). These findings were ratified when the sample was augmented to 213 brains (Brayne et al., 2009) where 22% of the brains of participants clinically diagnosed as having dementia had mixed pathologies. White et al. (2002) in the Honolulu-Asia Aging study also presented similar findings on 285 donated brains where 16% of the clinically demented decedents had mixed pathologies. The Hisayama study, based on 275 autopsied brains, reported an even higher proportion of mixed pathologies (34%) among those with clinical dementia (Noda et al., 2006). Also, the neuropathology group from the CFAS cohort have emphasized the high prevalence of vascular pathology in this population and the common occurrence of a mixture of both AD and vascular pathology (Neuropathology Group, 2001).

Part 2 Review of major studies in old age psychiatry



This section summarizes some of the most important and informative epidemiological studies on cognitive and other mental changes in old age. Three main types of study are discussed: combined studies; studies that have used a synthesis of the literature with data from several sources; and longitudinal studies. There are several difficulties in examining epidemiological studies in the context of dementia. For example, some studies report on overall dementia estimates, whereas others restrict their reports to AD, using this term almost as a synonym of dementia, disregarding the existence of diseases and mixed pathologies.

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Combined studies

In this section, the following combined studies for the epidemiology of dementia will be presented: the EURODEM initiative; and the 10/66 Dementia Research Group.

The EURODEM initiative

In the early 1990s, there was a collaborative initiative of all major European groups working on the epidemiology of dementia, organized by EURODEM, EC Concerted Action on the Epidemiology of Dementia (Hofman et al., 1991). A total of 20 centres took part and contributed original data of 23 population studies published between 1980 and 1990, from which 12 were included in the analysis. Those studies which were methodologically similar and suitable for comparison were selected to describe geographical differences and to provide an overall estimate of the prevalence of dementia in Europe. The study confirmed the steep rise of dementia prevalence with age, showing that within 5-year age groups, the prevalence of dementia almost doubles from the age group of 65–69 onwards. No major differences were noted regarding sex; however, the overall estimates were somewhat larger for men than for women until the age of 75 years, and somewhat larger for women over the age of 75 years. These patterns were similar across the 12 studies (Hofman et al., 1991). Only 2% of cases were found in those less than 65 years.

An incidence phase of the EURODEM initiative was conducted and included results of analyses based on pooling the data from the studies conducted in Denmark, France, the Netherlands, and the United Kingdom (Launer et al., 1999). In Denmark, the Odense Study (Andersen et al., 1997) had a baseline cohort of 3346 persons; in France, the PAQUID study (Letenneur et al., 1994) included 3777 individuals at baseline; in the Netherlands, the Rotterdam study (Ott et al., 1995) had a baseline cohort of 5265 persons with age starting from 65 years; and in the United Kingdom, the MRC-ALPHA study (Saunders et al., 1992) had a baseline cohort of 5222 participants. In this pooled analysis of individuals aged 65 years and older, 528 incident dementia patients were reported over 28,768 person-years of follow-up. Incidence rates for dementia were similar across studies and increased with age; at 65 years of age, the incidence rate for dementia was 2.5 (95% CI = 1.6, 4.1), and at 90+ years, the rate was 85.6 (95% CI = 70.4, 104.0) per 1000 person-years. The study investigated potential risk factors for dementia and found that current smoking and low levels of education increased the risk of dementia significantly. A history of head trauma with unconsciousness, female gender, and a family history of dementia did not increase the risk significantly.

The 10/66 Dementia Research Group

The 10/66 Dementia Research Group (<http://www.alz.co.uk/1066/>) brings together researchers with an interest in ageing in LMICs, including

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determination of the prevalence and incidence of dementia and non-communicable diseases (Prince et al., 2007).

Cross-sectional comprehensive one-phase surveys have been conducted of all residents aged 65 years and over from geographically defined catchment areas in ten LMICs (India, China, Nigeria, Cuba, Dominican Republic, Brazil, Venezuela, Mexico, Peru, and Argentina), with a sample size of between 1000 and 3000 in each site. Overall, 14,960 individuals completed the prevalence study. Response rates varied between 72% and 98% (Llibre Rodriguez et al., 2008). Two approaches were used for dementia diagnosis. The first was based on a regression equation developed in the 10/66 International Pilot Study that uses coefficients derived from the GMS/AGECAT (Copeland et al., 1986), the Community Screening Instrument for Dementia, and the 10-word learning task (Prince et al., 2003). This approach has been validated for cross-cultural settings and is sensitive to educational status (a large proportion of older aged individuals in LMICs have little or no education) and regional variation, particularly associated with diversity in language and culture. The second approach applied DSM-IV criteria directly (American Psychiatric Association, 1994). For diagnosis of dementia subtypes, the following criteria were used: NINCDS-ADRDA AD criteria (McKhann et al., 1984), National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) vascular dementia criteria (Roman et al., 1993), and DLB (McKeith et al., 1992).

10/66 Study: dementia

Across the 10/66 regions, dementia prevalence varied between 5.6% and 11.7%, using the regression equation. When DSM-IV criteria were applied directly, the prevalence varied between 0.4% and 6.4%. Prevalence determined by the 10/66 equation was higher at every site and generally double that estimated using direct application of the DSM-IV criteria (Llibre Rodriguez et al., 2008). Comparison of the prevalence of dementia reported in the EURODEM meta-analysis with that reported using the DSM-IV criteria in the 10/66 sites found large variation—the prevalence in urban Latin American sites was about four-fifths of that in Europe; the prevalence in the Chinese sites was just over half, and that in rural Latin American and Indian sites only between a quarter and a fifth (Llibre Rodriguez et al., 2008).

An incidence phase (3–5 years follow-up) was conducted in six of the study sites, including urban sites in Cuba, the Dominican Republic, and Venezuela and urban and rural sites in Peru, Mexico, and China. Of the 12,887 participants interviewed at baseline, 11,718 were free of dementia and 69% ($n = 8,137$) were re-interviewed, contributing 34,718 person-years of follow-up. The dementia incidence rate (per 1000-person years) was similar to that typically recorded in HICs but varied across country and with the diagnostic criteria used. When using the 10/66 equation, the incidence ranged from 18.2 (95% CI = 14.3–23.0, Peru) to 30.4 (95% CI =

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25.5–36.3, Mexico), and for the DSM-IV criteria, the incidence ranged from 9.9 (95% CI = 7.5–12.9, Venezuela) to 15.7 (95% CI = 12.2–19.8, Mexico) (Prince et al., 2012). In terms of risk factors, incidence was associated with age (increasing), gender (female), education (inverse association), having less assets (substantial heterogeneity in finding across sites), literacy, and poorer baseline cognitive function (assessed using verbal fluency and motor sequencing tasks).

10/66 Study: depression

Depression, anxiety, and co-occurrence of anxiety and depressive syndromes have been investigated among the 10/66 centres (Prina et al., 2011). Anxiety was measured using the GMS/AGECAT, and depression was assessed according to ICD-10 and EURO-D criteria.

The prevalence of depression according to the ICD-10 was reasonably consistent across Latin America and India (range 4.9–13.8%) but was much lower in the Chinese site. A similar pattern was also found for the distribution of anxiety (range, excluding China: 2.3–8.9%). The prevalence of co-occurring anxiety and depression ranged between 0.9% and 4.2% across sites. Having both disorders was linked to higher disability scores than having anxiety or depression alone. This has major implications for treatment outcome, which is found to be worse in individuals with comorbid anxiety and mood disorders, compared to individuals suffering from depression alone (Prina et al., 2011).

10/66 Study: summary

The 10/66 Dementia Research Group focuses on the study of dementia diagnosis among populations in LMICs. Their population-based surveys provide a unique resource for comparative descriptive research of not only prevalence and incidence, but also its effects, risk factors, costs, interventions, estimations of needs, and roles of racial mixture, micronutrient deficiency, and cardiovascular disease.

Synthesis of literature

In this section, the following studies for the epidemiology of dementia will be presented:

- Worldwide prevalence and incidence of dementia.
- Delphi consensus study.
- Meta-analysis of dementia prevalence and incidence.
- World Alzheimer Report 2015.

Worldwide prevalence and incidence of dementia

Fratiglioni et al. (1999) reviewed the prevalence and incidence data for dementia reported in the international literature from 1990 to 1998. In total, 36 prevalence (including studies with sites in: Europe, the United

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States, Canada, Japan, Korea, India, China, and Nigeria) and 15 incidence (including studies with sites in: Europe, the United States, China, and Taiwan) studies were identified. Worldwide dementia prevalence and incidence rates were found to increase with age. Worldwide prevalence was estimated to be 0.3–1.0 per 100 people in individuals aged 60–64 years, and 42.3–68.3 per 100 people in individuals aged 95 years and older. Incidence rates ranged from 0.8–4.0 per 1000 person-years in people aged 60–64 years and increased to 49.8–135.7 per 1000 person-years when the population was older than 95 years. Geographical variation in prevalence and incidence was low, with differences between countries largely reflecting methodological, rather than real, differences. Regarding dementia subtypes, AD was always the leading type of dementia in all continents. However, the relative proportions attributed to AD and vascular dementia seemed to differ among continents and multi-ethnic communities of Western countries. North America had the highest relative proportion of AD among all the dementing disorders (74.5%), whereas Asia had the least relative proportion of AD (46.5%). The prevalence of vascular dementia ranged from 10.0% in North America to 38.1% in Asia. Differences in diagnostic criteria and procedures might account for these inconsistencies.

Delphi consensus study

Alzheimer's Disease International convened an international group of experts to generate up-to-date evidence-based estimates for the prevalence of dementia for each world region (Ferri et al., 2005). The authors used the Delphi consensus method, which, in essence, derives quantitative estimates through the qualitative assessment of evidence where studies of widely different design and quality can be assessed. When published information is scarce, experts can make inferences using other data from comparable contexts. Although studies varied widely in quality, methodology, and dementia outcome definition, the only inclusion criterion was that the study should be population-based. They found that the seven areas with the largest number of people with dementia in 2001 were: China (5.0 million), the European Union (5.0 million), the United States (2.9 million), India (1.5 million), Japan (1.1 million), Russia (1.1 million), and Indonesia (1.0 million). They estimated that 24 million people had dementia in 2005 and that this amount would double every 20 years to 42 million by 2020 and 81 million by 2040, assuming no changes in mortality and no effective prevention strategies or curative treatments.

Meta-analysis—dementia prevalence

Prince et al. (2013) conducted a meta-analysis on the global literature on dementia prevalence published from 1980 to 2009 in 21 Global Burden of Disease regions. The search identified 147 studies (representing 135 publications), including studies from Western Europe, East Asia, the Asia Pacific High Income, North America, Latin America, South Asia, South East Asia, Australasia, the Caribbean, Central Europe, North Africa/Middle East, Western sub-Saharan Africa, Eastern Europe, and Southern

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sub-Saharan Africa. No eligible studies were identified for Central and Eastern sub-Saharan Africa or Central Asia. Prevalence of dementia was found to increase exponentially with age and in all regions, except North America and Asia Pacific, and men had a predicted prevalence ranging from 19% to 20% lower than women. Similar to the Fratiglioni et al. (1999) study, the estimated age-standardized prevalence of dementia in people aged ≥ 60 years varied little across regions (range between 5% and 7%), although some regions had lower (2.1% in West sub-Saharan Africa) and higher (8.5% in Latin America) estimates. Based on the figures, it was estimated that, in 2010, there were 35.6 million people with dementia worldwide, with the projected number estimated to double every 20 years to 48.1 million in 2020 and 90.3 million in 2040. These estimates are approximately 10% higher than those reported by the earlier Delphi Consensus Study described in the previous section.

Meta-analysis—dementia incidence

Jorm and Jolley (1998) conducted a meta-analysis of the age-specific incidence of all dementias, including AD and vascular dementia. The inclusion criteria were: case finding should be based on a field survey or studies of medical and social agencies, excluding purely hospital-based case register studies; age-specific incidence of dementia had to be reported for age groups spanning 10 years or less; the study had to involve a population-based sample, rather than volunteers; incidence rates had to be reported for mild or moderate dementia; and data needed to calculate the standard errors of incidence rates had to be available or accessible from the authors. The final analysis was based on data from 23 studies and showed that the incidence of both dementia and AD rise exponentially up to the age of 90 years, with no sign of levelling off, whereas the incidence for vascular dementia varied greatly. There was no sex difference in dementia incidence, but women tended to have a higher incidence of AD in very old age and men tended to have a higher incidence of vascular dementia at younger ages. East Asian countries had a lower incidence of dementia than European countries.

World Alzheimer Report 2015

The Alzheimer's Disease International's World Alzheimer Report 2015 was based on a series of updated systematic reviews conducted by an independent research group to collate and review all of the available evidence relating to the global prevalence, incidence, and costs of dementia (Alzheimer's Disease International, 2015). They reported the crude prevalence estimates of dementia in individuals aged ≥ 60 years in 2015 ranged from 4.7% in Central Europe to 8.7% in North Africa/Middle East (world estimate = 5.2%). Worldwide incidence was estimated at over 9.9 million new cases each year, with varying regional distribution: 4.9 million (49% of the total) in Asia, 2.5 million (25%) in Europe, 1.7 million (18%) in the Americas, and 0.8 million (8%) in Africa. The cost of dementia, including direct medical costs, social care costs, and costs of informal (unpaid) care, have been suggested to have increased by 35.4%

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from 2010 (US\$ 604 billion) to 2015 (US\$ 818 billion). The report stresses that research investment into dementia needs to be scaled up, with a focus on cure, care, treatment, prevention, and risk reduction.

Longitudinal studies

Numerous longitudinal studies on the epidemiology of depression and dementia, including its subtypes, have been undertaken in the last 50 years. We will present a selection of the main truly population-based longitudinal studies across the years to illustrate methods and findings. This cannot be comprehensive. In all of these studies, we will focus on the papers that disclosed figures for prevalence and incidence of dementia and depression, and comment on possible additional findings on those papers.

- Lundby Study.
- Iceland birth cohort.
- Reykjavik Study.
- Gothenburg Study.
- Cambridge City over 75s Cohort Study (CC75C)
- Framingham.
- Established Populations for Epidemiologic Studies of the Elderly (EPESE).
- Gospel Oak Study.
- Cognitive Function and Ageing Study I (CFAS I).
- Cognitive Function and Ageing Study II (CFAS II).
- Rotterdam Study.
- Vantaa 85+.
- Personnes âgées QUID (PAQUID).
- Italian Longitudinal Study of Ageing (ILSA).
- The Three-City study (3C).
- Newcastle 85+ Study.
- Epidemiological Clinicopathological Studies in Europe (EClipSE).

Lundby Study

The first and the longest comprehensive prospective study of an entire community, with a focus on psychiatric epidemiology, was conducted by Essen-Möller in 1947 (Essen-Möller et al., 1956). This study had a unique place in the field of not only epidemiology of old age psychiatry, but also epidemiology of psychiatry overall since it involved participants aged 15 years and over. The aim was to observe the entire population of a community in the south of Sweden, notionally called Lundby, to study individual traits and morbidity in a general population, not in patients. All but 1% of the 2550 adult inhabitants of Lundby aged 15 years and over

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were examined (Henderson and Jablensky, 2010). This cohort was further re-examined in 1957, 1972, and 1997. In addition to the psychiatric interview, and unlike most other surveys, information was obtained from multiple sources: face-to-face interviews, informants and community nurses, general practitioners, death registers, the Swedish psychiatric register, the national hospital inpatient register, and the local outpatient register. In 1972, the investigators were able to obtain sufficient information to reach a diagnosis on 99% of the cohort, and in 1997 on 94%.

The Lundby strategy is a marked contrast to today's large-scale surveys. Information was obtained by psychiatrists, who were free to explore the respondent's symptoms and behaviour at interview, rather than by lay interviewers who were required to complete a symptom checklist and follow a tightly scripted text from which they must not deviate.

Lundby Study: dementia

The prevalence of all-cause dementia in both sexes in the Lundby Study, according to age group, is shown in Table 4.1 (Hofman et al., 1991).

Table 4.1 Prevalence of dementia of all types in both sexes in the Lundby Study according to age group

Age group (years)	Prevalence (%)	Cases (n)	Group (n)
30-59	0.0	0	971
60-64	0.5	1	191
65-69	1.7	3	177
70-74	4.8	6	126
75-79	7.9	6	76
80-84	17.8	8	45
85-89	15.8	3	19
90-94	27.3	3	11
95-99	0.0	0	1

Source: data from Hofman, A., Rocca, W. A., Brayne, C., et al. (1991), The prevalence of dementia in Europe: a collaborative study of 1980-1990 findings. Eurodem Prevalence Research Group, *International Journal of Epidemiology*, 20 (3), 736-48.

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Male- and female age-standardized first incidence rates of dementia every fifth year from 1947 to 1997 are seen in Fig. 4.1. In both males and females, a trend of decreasing dementia incidence can be observed from 1947 to 1997 (Bogren et al., 2007). The data between waves were gathered from all available sources such as registers and case notes.

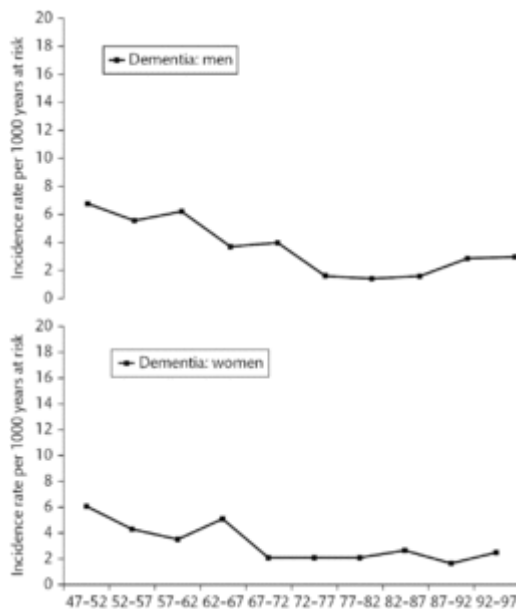


Fig. 4.1

First-incidence rates of dementia in the Lundby study.

Adapted with permission from Bogren, M., et al. Lundby revisited: first incidence of mental disorders 1947-1997. *Australian and New Zealand Journal of Psychiatry*, 41 (2): 178-86. Copyright © 2007, SAGE Publications. <https://doi.org/10.1080/00048670601109964>.

This finding was unexpected and may be explained by the fact that the study ran when different principles of classification were used, possibly affecting diagnostic conclusions, or even because there was a difference in study waves regarding the number of supplementary sources of information concerning outpatient care and key informants, which was greater in 1947-1972 than in 1972-1997 (Bogren et al., 2007). An alternative explanation is that it might be a genuine cohort effect, as the incidence of dementia could have fallen due to factors such as less medical comorbidity or healthier lifestyle.

Lundby Study: depression

The median age at first onset of depression was reported to be around 35 years, and the recurrence rate was about 40%. Transition to other diagnoses was registered in 21% of the total sample, alcohol disorders in 7%, and bipolar disorder in 2%. Five per cent committed suicide, with an increased risk of suicide associated with male sex and increased

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depression severity. Although figures are not specific for older individuals, the Lundby Study showed that after the first onset of depression, 6% of men and 10% of women developed an organic disorder or dementia (Mattisson et al., 2007).

Lundby Study: Summary

The Lundby cohort has been followed prospectively during a period of great transition in society, which encompasses increased welfare, urbanization, and a change of societal structures, including development of public health care and education, entrance of women into the labour market, birth control, changes in family structure, lessening of the cohesive power of the family, church, and community, and changing roles of men and women. Biological and physical factors have also undergone change, including changes of lifestyle (diet and tobacco use) and availability of medical care such as new drug therapies, as well as changes in the physical environment (Bogren et al., 2007). Moreover, with an increase in life expectancy, it is possible to distinguish two different profiles for the older old and the recent old.

Iceland birth cohort

The Iceland birth cohort consisted of all Icelanders born in the years 1895, 1896, and 1897, and focused on the investigation of psychiatric diagnosis. The study was completed in four phases: the first spanning from 14 to 61 years (Helgason, 1964); the second from 61 to 75 years; the third from 75 to 81 years; and the concluding phase extending from 81 to 87 years (Magnusson, 1989). Information on the mental health of each proband was collected from several different sources. In each phase, every general practitioner in the country was interviewed in a systematic manner by a psychiatrist, asking about mental symptoms of the probands in the cohort. Next, all records from every hospital and nursing home in the country were studied and cross-checked with the data provided by general practitioners. When it was not possible to collect sufficient information to make a psychiatric diagnosis, other key informants were contacted such as relatives, local nursing staff, or neighbours. This method of data collection is referred to as the indirect method, since the information on mental and physical health did not come directly from the persons.

Diagnoses of psychiatric conditions were divided into three groups, including the dementia syndrome, affective disorders, and other mental disorders. The accuracy of the information in the initial phases of this study depended on how well the informants knew the proband. In the last phase of the study, however, an interview scheme which covered the major symptoms and signs of mental disorders in the aged population was implemented to allow validation of the indirect method.

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Iceland birth cohort: dementia

The dementia syndrome was initially diagnosed using information acquired from probands and records. Individuals were categorized according to severity as either mildly or severely demented. At later study stages, the participant was interviewed using the shortened version of the GMS Schedule. This allowed psychiatric diagnoses based on the computerized program AGE CAT (Copeland et al., 1986). Comparison of dementia prevalence across methods indicated a tendency of the indirect method to over-diagnose. The average age was 87 years. Indeed, 46% of participants considered to have dementia by the indirect method did not according to AGE CAT, whereas only 3% of the probands diagnosed as not having dementia by the indirect method were diagnosed as having dementia by AGE CAT (Magnússon, 1989). The prevalence of dementia according to the indirect method was 27%, and according to AGE CAT 17%. The most disagreement was in the group of participants considered to have mild dementia.

When examining the course of mild dementia in this cohort, Magnússon and Helgason (1993) found that many cases diagnosed as mild dementia by the indirect method had no or very few cognitive symptoms when AGE CAT was applied. Almost 30% of cases of mild dementia diagnosed by the indirect method before the age of 75 years had no symptoms of dementia at the age of 81 years, and >10% continued to have mild symptoms. Similar results were found at the age of 87 years.

Iceland birth cohort: depression

The prevalence of depression according to the indirect method was 8.7%, and it was unaffected by age (Magnússon, 1989).

Iceland birth cohort: summary

The study demonstrates how prevalence can be influenced substantially by information sources. While indirect methods have their advantages (e.g. avoid retrieval problems in patient groups), within the context of psychiatric illness, reliability of diagnoses derived from indirect data is questionable. Indeed, depression and dementia were, in many cases, not known to the family doctor (Magnússon and Helgason, 1993).

Reykjavik Study (Age, Gene/Environment Susceptibility study: AGES-Reykjavik)

The Reykjavik Study started in 1967 and comprised a random sample of 30,795 participants born in 1907–1935 in Reykjavik, Iceland (Harris et al., 2007). The study was performed in six waves (1967–1969, 1970–1972, 1974–1979, 1979–1984, 1985–1991, and 1991–1996), and the study sample was divided into six groups by birth date within each month. Each group was invited to participate in specific waves of the study. One group attended at all waves, another at two, and the remaining only once. In 2002, 11,549 participants were still alive and 5764 were re-examined

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during 2002–2006, as part of the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study (AGES I). In this sub-study, the oldest group of the original study was not recruited. The response rate was 72%. From 2007 to 2011, there was a follow-up examination of all surviving participants who agreed to participate (AGES II). The AGES-Reykjavik Study aimed to evaluate the common mechanisms leading to diseases in neurological, cardiovascular, musculoskeletal, and metabolic systems. Participants underwent comprehensive assessments, which included a questionnaire, a clinical examination, a cognitive battery, and imaging of the brain and retina (Harris et al., 2007).

Reykjavik Study: dementia

Dementia case ascertainment followed a 3-step procedure (Qiu et al., 2010). All participants were screened using the MMSE (Folstein et al., 1975) and Digit Symbol Substitution Test (DSST) (Wechsler, 1981). Screened positives on either of the tests were administered another more complete diagnostic test battery. Those who screened positively on the Trails A and B (Reitan, 1992) or the Rey Auditory Verbal Learning Test (Rey, 1958) went for a final assessment that included a proxy interview and a neurological examination. A diagnosis of dementia and its subtypes was made by means of a consensus, including a geriatrician, a neurologist, a neuropsychologist, and a neuroradiologist. Dementia was diagnosed according to the guidelines of the DSM-IV (American Psychiatric Association, 1994). AD, according to the criteria of the NINCDS-ADRDA (McKhann et al., 1984) and vascular dementia followed the criteria of the State of California AD Diagnostic and Treatment Centers (Chui et al., 1992). Of the 3906 participants, 132 (3%) were diagnosed with dementia, including 66 with AD, 31 with vascular dementia, and 20 with both. The group also explored if microvascular damage, indicated by cerebral ‘microbleeds’ (imaging detected excess iron, possibly due to small haemorrhages) and retinal microvascular signs, was associated with cognitive impairment and dementia. People with multiple cerebral ‘microbleeds’ had lower scores on tests of processing speed and executive function, and this difference was greater if there were multiple cerebral ‘microbleeds’ in deep hemispheric or infratentorial areas. All these associations were independent of major cardiovascular factors, white matter hyperintensity, and cerebral infarcts.

Reykjavik Study: depression

Data on depressive symptoms were collected on the AGES-Reykjavik Study and included the Geriatric Depression Scale (GDS) (Yesavage, 1988), depression history, and medications. History of major depressive disorder (MDD), including age at onset and number of episodes, and MDD in the past 2 weeks were diagnosed according to DSM-IV criteria using the MINI International Neuropsychiatric Interview. A prevalence of lifetime history of MDD was reported at 4.5%; 1.5% had a current diagnosis of MDD (i.e. in the past 2 weeks) and 3.0% had a past, but no current, diagnosis (Geerlings et al., 2013). Current MDD was found to be

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associated with higher levels of global brain atrophy (Geerlings, 2013). The prevalence of MDD was also found to be higher in men with deficient (<30 nmol/L) versus adequate (≥ 50 nmol/L) serum vitamin D levels (3% versus 1%), but not in women (Imai et al., 2015).

Reykjavik Study: summary

This large population-based cohort has made several contributions to the understanding of risk factors for myocardial infarcts and cancers (Harris et al., 2007). Extension of the data collected as part of the AGES-Reykjavik Study will allow examination of genetic susceptibility and gene/environment interactions, as these contribute to phenotypes common in old age.

Gothenburg Study

In 1986–1987, all 85-year-old people born between 1 July 1901 and 30 June 1902 in Gothenburg, Sweden, and registered for census purposes in Gothenburg were invited to take part in a health survey. This study was conducted as part of a series of longitudinal gerontological population studies (Rinder et al., 1975). Participants from both the community and institutions were invited. Some of the later publications from this group disclose amalgamated results from this cohort and the study of women in Gothenburg, 1968–1969 (Bengtsson et al., 1973).

Gothenburg Study: dementia

A systematic subsample of 826 individuals underwent psychological and psychiatric examination comprising questions about background factors, ratings of psychiatric symptoms and signs, ratings of signs common in dementia, and tests of mental functioning. Response rate was 63% ($n = 494$). After examination, an interview with a close informant was carried out (Skoog et al., 1993). There were 147 cases of dementia, according to the DSM-III-R criteria (American Psychiatric Association, 1987), and a prevalence of 30%. Subjects with dementia were further investigated with CT scans and classified into subtypes of dementia—AD, according to the NINCDS-ADRDA classification (McKhann et al., 1984), was present in 43% of the participants; vascular dementia based on the criteria proposed by Erkinjuntti et al. (1988) was found in 47%, and dementia due to other causes was diagnosed in the remaining 9%. The 3-year mortality rate was 23% in subjects without dementia, 42% in patients with AD, and 67% in patients with vascular dementia. Individuals diagnosed as having mixed dementia were included in the vascular dementia category. The population at risk comprising 347 individuals was re-evaluated 3 years later (Aevarsson and Skoog, 1996). Of these, 188 (54%) took part in a neuropsychiatric examination at the age of 88 years. Information on 132 withdrawals (deceased and refusals) was obtained from medical records or other sources. Sufficient information was thus obtained on 320 participants (92% of the population at risk). Sixty-three (20%) developed dementia during the study period. Of these, 42 cases were diagnosed from the neuropsychiatric examination, and 21 deceased or refusals from

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medical records or other information. The incidence of dementia was 90/1000/year, of which the incidence of AD was 36/1000/year and vascular dementia 39/1000/year (Aevarsson and Skoog, 1996).

The group also investigated the role of blood pressure on dementia at 75, 79, and 85 years (Skoog et al., 1996) in participants free from dementia at 70 years. They found that participants who developed dementia at ages 79–85 years had higher systolic and diastolic blood pressures at 70 years of age. However, just before dementia onset, blood pressure declined and was then similar to, or lower than, that of participants without dementia. Although the sample was representative of survivors at age of 79 years, only 11 participants had dementia, and at age 85 years, 18 had dementia, which makes it difficult to extrapolate these findings. The group further investigated this relationship in a different, but larger, cohort and published similar findings (Joas et al., 2012).

Gothenburg Study: depression

The contribution of this cohort in terms of depression was based on an investigation of the relation between depression and the 3-year incidence of first ever stroke. The diagnosis of depression was made according to the DSM-III-R (American Psychiatric Association, 1987) criteria and included the categories of major depression, dysthymia, and depression not otherwise specified. The diagnoses were based on symptoms during the month preceding the examination and observed symptoms during the psychiatric examination. Of all 85-year olds, 93 had a history of stroke and 19% were diagnosed with depression. Depression at baseline [hazard ratio (HR) = 2.7; 95% CI = 1.5, 4.7] was related to an increased incidence of first ever stroke during follow-up. Depression increased the stroke risk not only among participants without dementia, but also among those with dementia. However, a stroke history at age 85 years (baseline) was not associated with clinical depression.

Gothenburg Study: summary

This study emphasises the magnitude of dementia in the very old showing that almost 10% of persons between the ages of 85 and 88 develop dementia each year. This cohort showed a high prevalence and incidence of vascular dementia with the caveat that clinically defined mixed dementias were included in the vascular dementia diagnosis. Depression was quoted as a predictor of stroke.

Cambridge City over-75s Cohort Study (CC75C)

The first cohort study especially devoted to investigating dementia from a population perspective and determining the clinico-pathological correlates of dementia was the CC75C (<http://www.cc75c.group.cam.ac.uk>). The original prevalence phase of the study is known as the Hughes Hall Project for Later Life, and the incidence survey, which was launched 2 years later, is known as the Cambridge Project for Later Life (Fleming et al., 2007). The study began in 1985. A

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representative sample of 2609 individuals aged 75 years and over living in Cambridge city, UK were surveyed (O'Connor et al., 1989)—approximately one-third of all residents in this age range. All people in this age group in six family practices were approached and one in three from a seventh practice. Respondent rate was 95% and 40% of the oldest old in Cambridge took part (Brayne et al., 1992), so the sample was representative of the whole population in terms of age distribution, sex, and accommodation according to the Office of Population Censuses and Surveys (OPCS).

Each survey has included a detailed cognitive assessment, including at least the MMSE (Folstein et al., 1975), usually its extended version, and, in the majority of interviews, the Cambridge Cognitive Exam (CAMCOG) (Roth et al., 1986). Sub-samples have had detailed psychiatric assessment using the CAMDEX, detailed neuropsychological assessment, informant interview, and additional tests.

A consensus diagnosis for dementia status at death was made, consistent with the DSM-IV (American Psychiatric Association, 1994) criteria, using post-mortem review of all interviews, including proxy informant data, death certificates, and retrospective informant data after death, but blinded to neuropathology findings. Dementia was rated by severity and, where possible, subtypes were identified (Brayne et al., 2009). The study is still ongoing, representing an exceptional duration for a population-based cohort, although there are now very few survivors, all aged over 100.

CC75C: dementia

The total prevalence of all grades of dementia was 10.5%. Estimates of prevalence increased with age, including: 4.1% (75–79 years), 11.3% (80–84 years), 19.1% (85–89 years), and 32.6% (90 years or over) (O'Connor et al., 1989). Annual incidence rates for dementia also increased, with age approximately doubling every 5 years: 2.3% for participants initially aged 75–79 years, 4.6% for participants aged 80–84 years, and 8.5% for participants aged 85–89 years (Paykel et al., 1994).

CC75C: depression

Using questionnaire information, diagnoses according to the DSM-III-R criteria (American Psychiatric Association, 1987) were made. In addition, the interviewing clinician rated each person for 'severity of depressive symptoms' on a 5-point scale: none, minimal, mild, moderate, and severe (Girling et al., 1995). The population's estimated prevalence of MDD, based on the DSM-III-R criteria, was 2.4% (95% CI = 0.9%, 4.0%) and was 3.0% based on the CAMDEX criteria (95% CI = 0.7%, 5.3%). Five per cent of persons diagnosed as having dementia according to the CAMDEX criteria also received a diagnosis of depression. Around one in five people with dementia were rated as mildly or moderately depressed (Girling et al., 1995).

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CC75C: neuropathology

Using data from the brain donation programme, neuropathological analyses on tissue from a representative sample of the older population have been undertaken. The neuropathological protocol was based on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) method, with additional features to allow Braak staging of neurofibrillary pathology. The first 101 brains were reported by Xuereb et al. (2000), with half having developed dementia by death. The median age group was 86–90 years. This study found that tangles and neuritic plaques were highly inter-correlated. Significant, but weaker, correlations were also found between plaques and vascular amyloid, plaques and white matter pallor, tangles and vascular amyloid, and tangles and white matter pallor. Microvascular infarcts showed no relationship to any of these measures (Xuereb et al., 2000).

Results after over 200 donations had occurred have also been reported (Brayne et al., 2009). The overall burden of pathology was generally high across all participants, with most brains showing sufficiently extensive lesions to suggest a pathological classification of dementia, whether or not the donor had been clinically demented before death. However, participants with a clinical diagnosis of dementia did generally have a greater burden of pathology than those without dementia.

CC75C: summary

The main contribution for our understanding from this genuinely population-based study with substantial numbers of brains was the heterogeneity of lesions found in very old populations. Further, there was considerable overlap in the pathologies found in the demented and non-demented groups, and the pathological overlap between those diagnosed as having different subtypes of clinical dementia. This indicates that when assessing dementia during life, particularly in the older old, a focus on a single pathology has limited utility.

Framingham

Established in 1948, the Framingham study (Dawber et al., 1951) began as a longitudinal population-based cohort study of cardiovascular disease and associated risk factors, which enrolled 5209 volunteers (55% woman). Comprehensive physical examinations of the Framingham cohort have been obtained on a biennial basis. During biennial examination 14 or 15 (January 1976 through to March 1978), a dementia-free inception cohort was established. Among 2828 persons who were seen for physical examination, the response rate was 75% and complete data were available for 1085 participants aged 65 years or older who agreed to complete a brief neuropsychological screening battery (Linn et al., 1995). Starting with examination 17 (1982/1983) and on all successive biennial examinations, the MMSE was administered. Participants falling below age and education-adjusted levels were evaluated by a neurologist and a neuropsychologist to determine if dementia was present and, if so, to

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ascertain the dementia type. By using the criteria of Cummings and Benson (1986), dementia was considered to be present by the neurologist if the participant demonstrated a compromise in at least three areas of mental activity, including language, memory, visuospatial skills, personality or behaviour, and cognition, and if there was no disturbance in consciousness. Dementia severity was judged by criteria similar to those in the DSM-III-R (American Psychiatric Association, 1980). A neuropsychologist who was unaware of the dementia diagnosis made by the neurologist also saw the participants. If a person's performance was impaired on at least three of the seven neuropsychological tests used, they were considered to have cognitive impairment consistent with dementia. Dementia was considered present by the panel if the following three criteria were met: (1) cognitive impairment—if the neurologist found moderate or severe dementia to be present and the neuropsychologist independently confirmed the presence of cognitive impairment consistent with dementia; (2) cognitive decline—evidence that the person had definite deterioration in cognition from a pre-existing level of functioning; and (3) duration of cognitive impairment of at least 1 year (Linn et al., 1995).

Framingham: dementia

The prevalence of dementia was 30.5/1000 for men and 48.2/1000 for women and increased with advancing age. Cases of probable AD constituted 55.6% of all dementia cases. The prevalence of AD was 11.7/1000 for men and 30.1/1000 for women and also increased with advancing age. Prevalence of dementia and probable AD was greater for women than men. The female-to-male ratio of prevalence for cohort members aged 75 years and older was 1.8 for all cases of dementia and 2.8 for cases of probable AD (Bachman et al., 1992).

To determine the incidence of dementia and AD (Bachman et al., 1993), people previously free of dementia and falling below the 1-standard deviation (SD) cut-off score on screening tests were evaluated further to verify if dementia was present and, if so, the type of dementia, following the procedure described earlier. All new cases arising in this cohort over a maximum of 10 years of follow-up were ascertained. The incidence of dementia increased with age, doubling in successive 5-year age groups. Dementia incidence rose from 7.0 per 1000 per year at ages 65–69 to 118.0 per 1000 at ages 85–89 for men and women combined. The incidence of probable AD also doubled with successive quinquennia from 3.5 at ages 65–69 to 72.8 per 1000 at ages 85–89 years. Incidence of dementia and probable AD did not level off with advanced age and was not different in men and women.

Framingham: depression

In 1990, at the start of the 22nd biennial examination cycle, 1753 people from the original cohort were still alive. Of these, 1166 (67%) attended the 22nd biennial examination and, among them, 949 (81%; 604 women

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and 345 men) were dementia-free and were assessed for depressive symptoms. These participants were followed for up to 17 years (average follow-up 8 years) for incident dementia to examine the association between depressive symptoms at baseline and the risk of incident dementia (Saczynski et al., 2010).

During the 17-year follow-up period, 164 participants developed dementia; 136 of these cases were AD. A total of 21.6% of participants who were depressed at baseline developed dementia, compared with 16.6% of those who were not depressed. Depressed participants, defined by scores of at least 16 on the Center for Epidemiologic Studies Depression (CES-D) Scale (Radloff, 1977), had >50% increased risk for dementia (HR = 1.72; 95% CI = 1.04, 2.84) and AD (HR = 1.76; 95% CI = 1.03, 3.01). Results were similar when participants taking antidepressant medications were included. For each 10-point increase on the CES-D Scale, there was a significant increase in the risk of dementia (HR = 1.46; 95% CI = 1.18, 1.79) and AD (HR = 1.39; 95% CI = 1.11, 1.75). Results were similar when persons with possible MCI were excluded.

Framingham: summary

Another important contribution of the Framingham study to the field of dementia was the estimation of the lifetime risk of dementia. A group of 2794 participants without dementia who were 65 years or older were followed up for a maximum of 29 years (42,233 person-years). There were 400 cases of incident dementia of all types and 292 cases of incident AD. The lifetime risk of any dementia was estimated at more than 1 in 5 in women and 1 in 6 in men, and the lifetime risk of AD about 1 in 5 for women and 1 in 10 for men (Seshadri et al., 2006).

Established Populations for Epidemiologic Studies of the Elderly (EPSE)

The goals of the EPSE project were to describe and identify predictors of mortality, hospitalization, and placement in long-term care facilities and to investigate risk factors for chronic diseases and loss of functioning. The survey elicited information from persons 65 years of age and older in four different geographic locations in the United States: East Boston, New Haven, Iowa, and North Carolina. The baseline data cover demographic characteristics (age, sex, race, income, education, marital status, number of children, employment, and religion), height, weight, social and physical functioning, chronic conditions, related health problems, health habits, self-reported use of dental, hospital, and nursing home services, and depression.

In East Boston, individuals eligible for the study were identified through a total community census performed concurrently with a baseline interview in 1982. In Iowa, the sample was not truly populational since interviews were attempted with all eligible individuals enumerated using a list from the area's Agency on Aging, supplemented by additional listings from local informants. New Haven used a stratified random sample of clusters

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of households. The sample was stratified for three types of residence, including: public housing for the older population, private housing for the older population, and elsewhere in the community. Males were over-sampled to attempt to achieve balance in the sex distribution of the sample. In North Carolina, area sampling was used in the first stage of the design to obtain a sample of 1980 census blocks, block clusters, and enumeration districts. The sample was designed so that it would consist of at least 50% black older persons. The investigation of dementia was conducted using the sampled members of the Duke EPESE (Heyman et al., 1991), which focused on five adjacent counties, one primarily urban and the other four mostly rural, in the Piedmont area of North Carolina. The last stage of the sampling procedure consisted of selecting one older person at random from each household in which there were residents aged 65 years and older. Of 5223 persons selected for the sample, 4164 were successfully interviewed, yielding a response rate of 80%. Of these, 2259 (54%) were black and 1905 (46%) were non-black. The sampling design permitted the development of weights, which took into account age, sex, race, geographic location, the number of old people in the household, and non-response, so that it was possible to project data from the Duke EPESE sample to the same-age population of other areas.

A brief screen of cognitive function—the Short Portable Mental Status Questionnaire (SPMSQ) (Pfeiffer, 1975)—was administered at baseline, which, according to the authors, by using the adjusted scores, little race or education bias is found. The case finding procedure involved trichotomization of the SPMSQ scores, i.e. the total EPESE sample was divided into persons with scores below the cut-off for cognitive impairment, those with one point better than the cut-off, and finally, those with two points better than the cut-off. The selected participants were seen by a neurologist who administered a semi-structured interview which involved a medical and psychiatric history and a physical and neurological examination. Based on these measures, a diagnosis of dementia, and specifically of AD, was made, using the DSM-III and the NINCDS-ADRDA (McKhann et al., 1984). The severity of dementia, when present, was rated on the Clinical Dementia Rating scale, which includes information for rating the individual in six cognitive and behavioural categories: memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care (Hughes et al., 1982). The project attempted to compare the prevalence and incidence of dementia between black and all other participants.

EPESE: dementia

For the 1986 and 1987 survey, when the baseline data were collected, the estimated prevalence of dementia was 8.9% for black men, 19.9% for black women, 3.3% for white men, and 2.9% for white women. The overall estimated prevalence for blacks and whites were 16% (95% CI = 7.9, 24.1) and 3.0% (95% CI = 0, 6.9), respectively (Heyman et al., 1991). The overall prevalence of dementia among blacks was significantly higher than in whites. However, the same difference was not found in the 1989

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and 1990 survey where the prevalence of dementia was 7.0% (95% CI = 2.1, 11.9) for blacks and 7.2% (95% CI = 2.2, 12.2) for whites. Prevalence for black men (7.8%; 95% CI = 0.1, 15.5) exceeded that for black women (6.6%; 95% CI = 0.3, 12.9), but gender prevalence values for whites were reversed (men: 4.4%, 95% CI = 0.0, 10.3; women: 8.7%, 95% CI = 1.5, 16.0) (Fillenbaum et al., 1998).

The 3-year incidence of dementia between the two surveys 1986–87 and 1989–90 was found to be 5.8% (95% CI = 2.6, 9.0) for blacks and 6.2% (95% CI = 2.7, 9.7) for whites. Neither race nor gender differences were significant (Fillenbaum et al., 1998).

EPESE: depression

To address the influence of socio-economic variables in the association between racial differences and late-life depression, basic needs, income, and education variables controlling for sex, age, and functional status were examined (Sachs-Ericsson et al., 2005). Data for this analysis were derived from the Duke EPESE. Before adjusting for socio-economic variables, African American older people had more depressive symptoms than white older participants in the cross-sectional analyses. However, after the inclusion of socio-economic variables, the relationship was inverted, such that white Americans were significantly more likely to endorse depressive symptoms than African Americans. In the longitudinal analyses, after controlling for baseline depressive symptoms, race was unrelated to depressive symptoms 3 years later.

EPESE: summary

The study highlights the importance of race and demographic and socio-demographic factors in determining estimates of disease prevalence and incidence. These findings reinforce that there is room for improvement of chronic conditions by reducing socio-economic disparities.

Gospel Oak Study

This is a longitudinal prospective study, based on the Gospel Oak electoral ward, North London (Livingston et al., 1990a). Its main purpose was to detect those persons likely to be suffering from dementia or depression or to be impaired in performing activities of daily living. The electoral ward had an estimated population of 6136 living in 3000 households and had higher rates of most indices of deprivation than the average for England and Wales at the time.

Interviews took place in 1987. The sample consisted of all women aged over 60 years and men over 65 years who were residents of this area. All participants were interviewed using the Standard Comprehensive Assessment and Referral Evaluation (CARE) (Gurland et al., 1984). This instrument is composed of six screening scales that assess depression, organic brain syndrome, subjective memory impairment, sleep disorder, somatic symptoms, and activity limitation. The depression and dementia

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scales have been further refined to become depression and dementia diagnostic scales (the Dementia Diagnostic Syndrome scale) which refer to syndromes of cognitive impairment and depressed mood severe enough for further clinical intervention (Kay et al., 1964). The final sample for interview consisted of 932 participants (women over 60 years, men over 65 years) who represented 15.2% of the ward population. The response rate of available people was 87.2%.

Gospel Oak Study: dementia

On the six screening scales, 8% were identified as cases of organic brain syndrome, 27% as depressive cases, 25% with subjective memory complaints, 33% with sleep disorders, 32% with limitation in performing activities of daily living, and 24% with somatic symptoms. After refinement for identifying syndromes of cognitive impairment (the Dementia Diagnostic Syndrome scale), dementia prevalence at screening was estimated at 4.7%. However, this value increased to 7% when residents of the local authority home were included.

Eighty per cent of the 60 people initially identified by screening were further assessed using the GMS/AGECAT instrument (Copeland et al., 1986), a psychiatric interview, and neuropsychological testing (Livingston et al., 1990b). Among those participants, 43 were diagnosed as having dementia of any type, based on the psychiatric diagnosis. For the whole Gospel Oak population, the overall prevalence for dementia of any type was 6.1% (43/705). AD prevalence, according to the NINCDS/ADRDA criteria (McKhann et al., 1984), was 3.1% (22/705). Multi-infarct dementia (0.01%, 1/705), mixed dementia (0.7%, 5/705), and secondary dementia (0.7%, 5/705) were rare. In contrast, diagnosis based on the GMS/AGECAT resulted in a prevalence of organic caseness of 4% (28/705). The GMS/AGECAT was more likely to diagnose as 'organic' those participants whom the psychiatrists diagnosed as having AD. The total dementia prevalence as diagnosed by the psychiatrists was higher (6.1%) than that reported at screening (4.7%) where the prevalence was calculated according to the Dementia Diagnostic Syndrome scale.

In 1990, 502 participants were successfully re-screened using the Short CARE. Six per cent of the re-screened participants were identified as incident dementia cases, based on screening (Boothby et al., 1994), and 1.6% according to the Dementia Diagnostic Syndrome scale. However, by means of clinical diagnosis, the overall annual incidence of dementia in persons aged over 65 years was 2%.

Gospel Oak Study: depression

Depression varied according to the place of residence. A total of 17.3% (122) of the population living at home were classed as probably suffering from pervasive depression, as measured using the Depression Diagnostic Scale. Excluding those individuals who also were diagnosed as having dementia reduced the prevalence of depression to 15.9%. On the other

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hand, the prevalence increased to 18.5% when residents of the local authority home were included. Depression was not associated with age (Livingston et al., 1990a).

Gospel Oak Study: summary

Additional research questions within the framework of the Gospel Oak Study have focused on the association between cigarette smoking and alcohol drinking and incident cognitive impairment (Cervilla et al., 2000). Participants were asked whether they had ever smoked, and among those who smoked, currently or in the past, information was obtained on the average number of cigarettes smoked a day and on the number of years for which they had smoked. Participants were also asked about the amount of alcohol used before or after the age of 65 years. Current smokers were nearly four times more likely to be cognitively impaired than never-smokers or ex-smokers, after adjusting for baseline cognitive function, depression, occupational class, education, handicap, and alcohol consumption before and after the age of 65 years. Alcohol drinking was not a risk factor for incident cognitive impairment. The finding that current smokers, but not ex-smokers, are at higher risk of developing cognitive decline is of great public health relevance for smoking prevention and smoking cessation campaigns and policies targeting the prevention of cognitive impairment.

Cognitive Function and Ageing Study I (CFAS I)

CFAS is a multidisciplinary, multiphase, population-based study, which involved five sites with identical assessments: Cambridgeshire, Gwynedd, Newcastle, Nottingham, and Oxford. An additional site was based in Liverpool, but the sampling and interview structure were different. The study was designed to cover three main areas related to dementia and ageing, including epidemiology, neuropathology, and policy (Brayne et al., 2006). The fieldwork began in 1991 (Chadwick, 1992).

Background information on the demographics of the populations sampled was collected from the OPCS 1990–1991 census, to enable comparison with regional and national data. The population sample was drawn from the Family Health Service Authorities lists. These are registers of the general practitioners providing a near-total population enumeration in the areas chosen for study, including individuals living in institutions. Individuals aged 65 years and over were selected for participation.

Trained interviewers administered structured interviews at the respondents' homes, which included the GMS and the MMSE (Folstein et al., 1975), and basic information on residence, marital status, social class, and main occupation during working life (Elias et al., 1993); social and service contacts (Wenger, 1989); physical health and well-being, including vascular risk factors (Launer et al., 1992); activities of daily living, as measured by the Townsend Scale (Townsend, 1979); and regular medication use (prescribed and over-the-counter). CFAS I also includes a

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brain donation programme, with a total of 456 brains donated up to August 2004 (Matthews and Brayne, 2005).

From the five identical sites, 13,004 individuals were screened (85% response from the eligible sample). Following screening, a 20% sub-sample was selected, based on age and cognition, weighted towards the older and more cognitively frail, to complete a more in-depth interview shortly afterwards, with a repeat at 2 years. Further screening and assessment interviews with the whole sample who remained in the study were carried out (see <http://www.cfas.ac.uk> for full details on the study design) (Brayne et al., 2006).

The ALPHA Liverpool Study fits within the framework of the CFAS but started earlier than the other five centres (Saunders et al., 1993). The Liverpool Family Practitioner Committee central computerized list of general practice patients was used as a sample frame. From this list, all patients aged 65 years or over with Liverpool addresses were selected. To provide a check on the diagnosis and to enable subclassification of GMS/AGECAT organic disorder into dementia types, a sub-sample of individuals received a second-stage assessment and an informant interview conducted by psychiatrists. The informant interview consisted of the History and Aetiology Schedule (HAS), which is drawn upon by the HAS/AGECAT.

CFAS I: dementia

CFAS I has reported on the UK population prevalence and incidence of dementia, as well as extensively on cognition and MCI. In the population aged 65 years and over, the standardized (to England and Wales population estimates for 1991) dementia prevalence was estimated at 6.6% (95% CI = 5.9, 7.3). This was based on dementia defined as an AGECAT organicity rating scale of three and above. Dementia prevalence across the centres did not vary greatly, although there was some evidence of non-systematic fluctuation in individual age- and sex-specific groups.

Dementia incidence estimated between the first two waves of interviews increased with age, from 7.4 (95% CI = 3.6, 16.1) per 1000 person-years at age 65–69 years to 84.9 (95% CI = 63.0, 107.8) per 1000 person-years at age 85 years and above. The rate of increase for both sexes was marked and continued into the oldest age groups. It was estimated that approximately 180,000 new cases of dementia occur in England and Wales each year. There is no convincing evidence of variation across sites, and incidence rates did not reflect the variations in the prevalence of possible risk factors in these sites (Matthews and Brayne, 2005). CFAS has also provided profiles of cognition weighted back to the UK population, based on MMSE, extended MMSE, and CAMCOG scores [including total score and sub-domain scores of orientation, language (expression and comprehension), memory (learning, recent, remote),

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praxis, attention and calculation, and perception] (Huppert et al., 2005; Williams et al., 2003).

The scope and operability of 16 different terms reflecting cognitive decline intermediate to normal ageing and dementia, and quantification of their prevalence and longitudinal course of disease have also been undertaken (Matthews et al., 2008). Across the 16 definitions, prevalence estimates were found to vary substantially (range 0.1–42%). As expected, the prevalence tended to increase for those definitions that capture a broader state of impairment, including, for example, Subjective Memory Complaint (SMC) and criteria for Cognitive Impairment No Dementia (CIND), and was less frequent for more restrictive definitions, including Amnesic Mild Cognitive Impairment (A-MCI). Rates of progression to dementia also varied and tended to be low. Overall, dementia progression was highest for more broadly defined concepts and those that capture greater levels of cognitive decline, particularly in older individuals. Across definitions, at 2-year follow-up, most individuals had remained stable, reverted to normal, or developed impairment outside the intermediate range. In the neuropathological analysis, MCI was found to be associated with an increased risk of neurodegenerative and vascular pathologies (Stephan et al., 2011; Stephan et al., 2012).

In terms of risk factor analyses, CFAS has shown that a simple measure of self-rated health (SRH) was associated with a higher risk of death and functional and cognitive impairment. The associations remained after adjustment for age, gender, functional ability, and MMSE at baseline; comparing those who rated their health as excellent and good, HRs for risk of death and functional and cognitive impairment were 0.8 (95% CI = 0.8, 0.9), 0.6 (95% CI = 0.5, 0.7), and 0.7 (95% CI = 0.5, 0.9), respectively (Bond et al., 2006).

Results from the neuropathological analyses have found that multiple neuropathological features determine the overall burden of dementia, including mixed vascular and Alzheimer's lesions, together with other changes such as atrophy (Matthews et al., 2009; Neuropathology Group, 2001; Savva et al., 2009; Wharton et al., 2011). Furthermore, the relationship between the clinical manifestations of dementia and the neuropathological findings varies with age, such that there is considerable overlap in the burden of neuropathological features of AD between groups of the oldest old persons with dementia and those without dementia. Even in participants who died without dementia, the burden of Alzheimer's-type disease in the population increased with increasing age.

In the Liverpool centre, GMS interviews were obtained on 5222 (87%) of the 6035 in the study area. A total of 444 GMS/AGECAT organic cases were identified at phase 1 and a sample of these was randomly selected for re-interview at phase 2. Of the available 205 participants who were assessed by psychiatrists to verify the clinical diagnosis, dementia was diagnosed in 84% ($n = 172$) of the organic cases. At wave 2, 328 were

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diagnosed as cases of organic disorder (of whom 120 were from wave 1 and 208 were new cases), and 232 in wave 3 (of whom 54 were from wave 1 and 53 from wave 2, leaving 125 new cases). Comparison of the CIs for the age-specific rates by sex showed no significant sex difference for the incidence rates of undifferentiated dementia (Copeland et al., 1999).

CFAS I: depression

The age and sex prevalence of depression standardized to the 1991 population of England and Wales was 8.7% (95% CI = 7.3, 10.2). No relationship between depression prevalence and age was found. However, high deprivation, high disability, and two or more comorbid illnesses were associated with a greater prevalence of depression (McDougall et al., 2007). Some, but not all, previous neuropathology studies have found an association between depression and markers of neurodegenerative and non-AD pathology (Jellinger, 2009; Sweet et al., 2004; Thomas et al., 2001; Wilson et al., 2003). In the CFAS neuropathology resource, depression ($n = 36$ out of 153 non-demented participants at death) has been associated with subcortical Lewy bodies (Tsopelas et al., 2011). In contrast to early findings from other studies, no association was found between depression and cerebrovascular or Alzheimer's pathology, although depression was associated with neuronal loss in the hippocampus, as well as in some of the subcortical structures investigated (nucleus basalis, substantia nigra, and raphe nucleus) (Tsopelas et al., 2011). It is important to note that despite the strong statistical association with depression in the samples where subcortical Lewy bodies or neuronal loss were detected, these neuropathological features were relatively rare, and most cases of depression found in this sample were not associated with any subcortical pathology. This suggests that subcortical pathology may account for a small number of cases of late-life depression in the population.

In the ALPHA Liverpool Study, the relationship between depression and the risk of incident dementia was also investigated (Chen et al., 2008). The risk of dementia was significantly increased with level four depressive syndromes derived from the GMS/AGECAT. The multiple adjusted HR was 2.47 (95% CI = 1.25, 4.89) and 2.62 (95% CI = 1.18, 5.80) at 2- and 4-year follow-up, respectively. The effect was greater in younger participants.

CFAS I: summary

Estimates of prevalence and incidence of dementia, cognitive decline, and depression from the CFAS I represent true population estimates due to study design. This has important implications for gauging the consequence of each disease (e.g. burden of care, cost) from a true population perspective.

Cognitive Function and Ageing Study II (CFAS II)

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CFAS II builds on the design and infrastructure of CFAS I and consists of centres in Cambridgeshire, Newcastle, Nottingham, and CFAS Wales: Gwynedd and Swansea. Recruitment began in 2008, and the study provides data on generational and geographical differences, including people in institutions. It also provides important baseline information on older people aged 65–84 years in 2008–2011 who will reach the age of greatest frailty during the 2020s, when the peak in the number of people aged 85 years or over is expected and at a time when major therapeutic interventions for dementia could be expected to have an effect.

Both CFAS I and CFAS II had identical designs and methods, apart from a change from a two-stage design with CFAS I to a one-stage design with CFAS II. In CFAS I, the first phase was a screening process, which identified a subset of individuals who underwent diagnostic assessment. CFAS II combined the screening and assessment phases. In total, 7796 individuals (14,242 approached, 56% response) in Cambridgeshire, Newcastle, and Nottingham were interviewed at baseline (2008–2011). At 2-year follow-up, 5288 individuals were re-seen (2010–2013, 74% response).

CFAS II: dementia

CFAS II reported a UK prevalence of dementia of 6.5% ($n = 670,000$) (Matthews et al., 2013). A comparison of standardized prevalence across time showed a substantial decrease in the prevalence of dementia [odds ratio (OR) CFAS II versus CFAS I = 0.7, 95% CI = 0.6–0.9; $p = 0.003$, adjusted for age, sex, area, and deprivation status]. The overall decrease was driven by non-care settings and was not noted within people in care settings where the prevalence increased (OR = 1.7, 95% CI = 1.0–2.9; $p = 0.05$). Women had a consistently higher prevalence of dementia than men in all settings. This study provides compelling evidence that a cohort effect exists in dementia prevalence in that later-born populations have a lower risk of prevalent dementia than those born earlier in the past century in the UK.

The overall incidence of dementia was reported at 17.7 (95% CI = 15.2–20.9) per 1000 person-years (Matthews et al., 2016). When compared to the estimates of CFAS I (20.0 per 1000 person-years, 95% CI = 16.9–23.8), a reduction was observed [incidence rate ratio (IRR) = 0.8; 95% CI = 0.6–1.0; $p = 0.08$, Poisson regression, $n = 10,444$]. Gender differences were reported; the results appear to be driven by a decrease in the incidence seen in men (0.6, 95% CI = 0.4–0.9; $p = 0.007$), but not in women (1.0, 95% CI = 0.7–1.3; $p = 0.9$).

CFAS II: depression

Data on depression have been collected, but not yet analysed.

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CFAS II: summary

Over the last two decades, there have been major changes in the health of people aged 65 years and over, with longer life and reductions in risk factors (e.g. smoking), increases in protective factors (e.g. education), and better management of some health conditions (e.g. cardio-metabolic diseases). CFAS II has provided updated evidence for policy purposes. The study also provides an opportunity to investigate the implications of changes in morbidity and frailty on health itself, as well as the use of services and expenditure in health and social care in future.

Rotterdam Study

The Rotterdam Study is a single-centre, population-based, prospective, dynamic cohort study of individuals aged 55 years and over that started in 1990 in Ommoord, a suburb of Rotterdam. The main objective has been to investigate the prevalence and incidence of risk factors for chronic diseases in the older aged population, including cardiovascular, neurological, locomotor, and ophthalmologic diseases.

Baseline measurements were obtained between 1990 and 1993, and all participants were subsequently examined every 2–3 years. In total, 7983 (78%) persons took part, including 897 persons living in one of the six homes for older people. In 2002, another 3011 participants (55 years of age since 1990) were added to the cohort, which comprised a total of 10,994 persons. In 2006, the cohort was further expanded by 3932 persons aged 45 years and over. The total Rotterdam Study population encompasses 14,926 participants. In 1995 and 1999, random subsets of the Rotterdam Study underwent neuroimaging, and from 2005 onwards, MRI has been implemented into the core protocol of the Rotterdam Study. Up to January 2011, a total of 5886 MRI brain scans have been obtained, which include multiple scans from the same people (Ikram et al., 2011).

Regarding old age psychiatric conditions, the Rotterdam Study addresses questions about the prevalence and incidence of various types of dementia and Parkinson's disease, and also verifies the determinants of such conditions. Participants were screened for dementia using a brief cognitive test, including the MMSE and GMS. Once screened positively, participants were then seen by a physician with the CAMDEX, and those who were still suspected of dementia were examined by a neurologist, had a brain MRI, and were tested by a neuropsychologist. No interviews were done on those who screened negatively (MMSE scores 26–30).

Rotterdam Study: dementia

Of the 10,275 eligible individuals, 7528 (73%) were screened for dementia, of whom 6.3% were diagnosed as having dementia. Overall, 72% of the dementias were of Alzheimer's type, 16% were vascular dementia, 6% were Parkinson's disease dementia, and 5% were other dementias (Ott et al., 1995). At follow-up, 5571 (79%) participants were re-screened for dementia. The overall incidence was 10.7 per 1000

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person-years (Ott et al., 1998). Dementia subtype clinical diagnosis was determined in 98% of the cases. AD was diagnosed in 61%; mixed dementia of Alzheimer's with cerebrovascular disease was detected in 12%, vascular dementia in 14%, and other dementias in 13%.

Results from the neuroimaging data show that white matter lesions are related to impairment of subcortico-frontal functions (Breteler et al., 1994), but also that changes affecting the microstructural integrity of normal white matter before these can be visualized using conventional MRI are also associated with cognitive function (Vernooij et al., 2009b). Those changes, such as mean diffusivity and fractional anisotropy, correlate directly with the amount of myelin in the white matter and, to a lesser extent, also to axonal count. They can be measured using the diffusion tensor imaging technique in MRI.

Regarding cerebral 'microbleeds', their spatial distribution was found to follow the known topographic distribution of amyloid angiopathy implicated in AD (Vernooij et al., 2009a). They were present in one in five persons aged ≥ 60 years and in over one in three persons aged ≥ 80 years (Poels et al., 2010; Vernooij et al., 2008). Furthermore, the presence of these numerous 'microbleeds', especially in a strictly lobar location, was associated with worse performance on cognitive tests, even after adjustment for vascular risk factors and other imaging markers of small vessel disease (Ikram et al., 2011). These results suggest an independent role for 'microbleed'-associated vasculopathy in cognitive impairment.

Rotterdam Study: depression

Depressive disorders were assessed by a 2-step procedure that included completion of the Dutch version of the original CES-D Scale, and for those who screened positive for depressive symptoms, a clinical psychiatric evaluation was undertaken. A strong relationship was observed between severe coronary and aortic calcifications and depressive disorders (OR = 3.89, 95% CI = 1.55, 9.77; and OR = 2.00, 95% CI = 1.02, 3.96, respectively). Although the analysis cannot establish a causal role of atherosclerosis, due to the cross-sectional nature of the study, it provides evidence that a generalized atherosclerotic process is associated with late-life depression (Tiemeier et al., 2004).

Rotterdam Study: summary

The Rotterdam Study has extensive information from a wide variety of sources, such as biological and MRI-based data, that can be used to help untangle the association between health and health-related risk factors and poor mental health. The high prevalence with MRI scans has helped with understanding the association between white matter lesions and cognitive impairment.

Vantaa 85+

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The Vantaa 85+ study is a prospective population-based study, which was established in 1991 (Polvikoski et al., 1995). The study population included all individuals who were born before 1 April 1906 and were aged 85 years or over, living in the city of Vantaa in Southern Finland ($n = 601$). Clinical examination was possible on 553 (92%) participants, and a neuropathological examination on 304 (51%). A neurologist and a trained public health nurse performed the clinical evaluations, which included a structured general and neurological examination. Data were systematically collected on health, health-related behaviour, and medication. Cognitive function, depression, and functional abilities were also assessed. Survivors were re-examined in 1994, 1996, 1999, and 2001. The entire study population is now deceased.

Dementia was diagnosed using the DSM-III-R criteria, AD using the NINCDS-ADRDA criteria, and vascular dementia using the NINDS-AIREN criteria. Initial blood samples for DNA analysis were obtained from 550 of the 553 persons examined.

Vantaa 85+: dementia

AD was clinically diagnosed in 16% of the Vantaa 85+ cohort. In contrast, the prevalence of AD was 33% (Polvikoski et al., 2001) when defined neuropathologically according to the CERAD protocol (Mirra et al., 1991). Forty-one (55%) of the 74 individuals with neuropathological AD were either in the no-dementia group or had dementia non-Alzheimer's type clinically defined (Polvikoski et al., 2001). The incidence of dementia was 8.1 per 100 person-years (Ahtiluoto et al., 2010).

In this study, the authors also investigated the relation of diabetes to dementia, AD, and vascular dementia, based on the fact that population-based longitudinal studies have shown controversial findings regarding diabetes as an independent risk factor for dementia. When the prevalence of dementia was split among those with and without diabetes, no association was found between dementia and diabetes after adjusting for sex, age, education, cardiovascular conditions, and apolipoprotein E (APOE) $\epsilon 4$ allele frequency. However, the incidence of clinically defined dementia in participants free of dementia at baseline ($n = 355$) was almost twice as high in patients with diabetes (12.1 person-years, 95% CI = 8.5, 17.2) than non-diabetic (7.2 person-years, 95% CI = 5.7, 9.0) individuals, even after adjustments for age, sex, education, and APOE $\epsilon 4$ status (Ahtiluoto et al., 2010). One possible explanation for the difference between the findings for prevalence and incidence is that the dementia duration was shorter in diabetic, compared to non-diabetic, participants, probably due to the diabetes-related increase in mortality.

Regarding the neuropathological findings, the proportion of individuals with β -amyloid and neurofibrillary tangles was lower in diabetic, compared to non-diabetic, individuals. In contrast, the proportion of participants with cerebral infarctions was significantly higher in diabetic,

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compared to non-diabetic persons, even after adjustments for age at death, gender, education, APOE, and dementia status.

Vantaa 85+: depression

Depressive symptoms were investigated using the Zung Depression Status Inventory (DSI) (Zung, 1972), which is a 20-item semi-structured, interviewer-rated depression instrument, with scores ranging from 25 to 100. Higher scores indicate more depressive symptoms. In the general population aged 85+ years, there was a very low prevalence of depression (1.1% for clear-cut clinical depression, and 4.1% for minimal to mild depression). Among participants with dementia, vascular dementia was significantly more common in individuals with higher depression scores (40 points or more on the Zung DSI). There was no association between Zung DSI scores and dementia severity.

Vantaa 85+: summary

The Vantaa 85+ study is one of the few autopsy-controlled, prospective, and population-based studies available on the prevalence of dementia in the very old population.

Personnes âgées QUID (PAQUID)

Paquid was the first large French epidemiological study on dementia. It is an interdisciplinary study designed to investigate cerebral and functional ageing. Residents living in two administrative areas of South-Western France (2797 in Gironde and 1504 in Dordogne) were randomly chosen from the electoral lists. A cohort of 3777 participants aged 65 years or over was interviewed. This cohort was complemented by a random sample of 380 institutionalized persons (Letenneur et al., 1993a).

Trained psychologists administered a standardized questionnaire at home. Baseline variables included socio-demographic factors, living conditions and habits, subjective health measures, dependence in activities of daily living (ADL) (Katz et al., 1970) and Instrumental Activities of Daily Living (IADL) (Lawton and Brody, 1969), and the Rosow and Breslow scale (Rosow and Breslau, 1966). Depressive symptomatology was also assessed. Intellectual functioning was examined through an extensive test battery that included an evaluation of global mental status, visual memory, verbal memory, verbal fluency, visuospatial attention, and simple logical reasoning.

After the psychometric evaluation, the psychologists completed systematically a standardized questionnaire, allowing determination of the DSM-III criteria for dementia. Patients who met the DSM-III criteria for dementia were seen by a neurologist who applied the NINCDS-ADRDA criteria to indicate the aetiology of the deterioration. Persons were re-evaluated following the same procedure as used for the baseline screening at 1, 3, and 5 years after the initial visit in Gironde, and 3 and 5 years after the initial visit in Dordogne. However, to improve the

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sensitivity of the detection of incident cases, respondents were selected for the neurological examination if they met the criteria for DSM-III-R dementia or if they had experienced a cognitive decline of >2 points on the MMSE.

PAQUID: dementia

Of the 5554 contacted subjects, 3777 (68%) agreed to participate in the study. The overall prevalence of dementia was estimated, based on the Gironde data, and was 4.3%. No difference was found between men and women (Letenneur et al., 1993b). Risk factor analysis found a greater risk for AD in people with fewer years of formal education. The overall incidence of dementia and AD was estimated at 1.59/100 person-years and 1.17/100 person-years, respectively. The incidence of AD was higher in women than in men after 80 years of age, whereas the incidence was higher in men before the age of 80 years. This different progression of the incidence according to sex was not found when other dementias were analysed (Letenneur et al., 1999). Numerous risk factors for dementia have been identified, with examples including a decreased risk in participants with lower psychosocio-economic precariousness, who remain/become active, and who have higher levels of engagement in social, physical, or intellectual pursuits (Dartigues et al., 2013; Foubert-Samier et al., 2014; Marioni et al., 2015; Ouvrard et al., 2017).

PAQUID: depression

To estimate the predictive relationship between depressive symptoms and incident dementia, Fuhrer et al. (2003) investigated 16,373 person-years of observation. The baseline prevalence of depressive symptomatology was 12.9% for men and 14.7% for women. The OR for the age-adjusted association between elevated depressive symptoms and onset of dementia was 2.0 (95% CI = 1.4, 2.8). However, after adjusting for gender, education, and cognition, the risk was reduced to 1.3 (95% CI = 0.8, 2.0), but these associations were significantly different between men and women. Men who had high depressive symptoms were more than three times as likely (OR = 3.5, 95% CI = 1.9, 6.5) than men with low depressive symptoms to develop incident dementia. This effect was not replicated for women. A possible explanation for this finding could be due to sex differences in vascular disease. It was found that the risk of dementia for men with hypertension who were depressed was 50% higher than for normotensive depressed men.

PAQUID: summary

PAQUID is an interdisciplinary study on cerebral and functional ageing, made up of a cohort of 3777 community residents living in two administrative areas of South-Western France. It has one of the longest follow-ups (i.e. 20 years). The epidemiological basis of the research programme is focused on the incidence, natural history, and risk factors of dementia.

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Italian Longitudinal Study of Ageing (ILSA)

ILSA is a population-based, longitudinal study aimed at determining the health status of people aged 65–84 years (Maggi et al., 1994). Common chronic conditions were investigated, along with potential risk and protective factors. ILSA was also designed to assess age-associated physical and mental functional changes. A random sample of 5632 people, stratified by age and sex using an equal allocation strategy, was gathered from the demographic lists of the registry office of eight municipalities including: Genoa, Segrate (Milan), Selvazzano-Rubano (Padua), Impruneta (Florence), Fermo (Ascoli Piceno), Napoli, Casamassima (Bari), and Catania. Baseline examination started in March 1992. Case identification for all conditions was based on a two-phase procedure, consisting of a screening phase, administered by lay interviewers, and, for those who screened positive, a clinical assessment run by specialists according to the condition. The final diagnosis of dementia was made according to the DSM-III-R criteria, for AD according to the NINCDS-ADRDA criteria, and for vascular dementia and other dementias according to the ICD-10. From the total population sampled, 5462 were eligible, 84% took part in the home interview, and 64% participated in the clinical examination (The Italian Longitudinal Study on Aging Working Group, 1997).

ILSA: dementia

Among the 3497 persons included in the baseline wave, the prevalence of dementia was 7.2% for women and 5.3% for men (The Italian Longitudinal Study on Aging Working Group, 1997). The follow-up phase was conducted on 2498 individuals free of dementia who were reassessed after a mean period of 3.8 years. The incidence rate of overall dementia was 12.5 per 1000 person-years (Di Carlo et al., 2002).

ILSA: depression

Depressive symptoms were investigated using the Italian version of the 30-item GDS (Yesavage et al., 1982). Further investigation sought to determine the possible impact of depressive symptoms on the rate of progression to dementia in individuals diagnosed with MCI (Panza et al., 2008). Of the 2963 participants, 139 prevalent patients with MCI were diagnosed at baseline. During the 3.5-year follow-up, 14 patients with MCI progressed to dementia, of whom nine had a GDS score of over 10. The association between depressive symptoms and the rate of progression to dementia in MCI was not significant [relative risk (RR) = 1.42, 95% CI = 0.48, 4.23].

ILSA: summary

This cohort has produced results on the prevalence of not only neuropsychological conditions such as dementia, but also general medical disorders such as myocardial infarction, angina, arrhythmia, congestive heart failure, peripheral arterial disease, hypertension, diabetes, stroke,

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parkinsonism, and disability. These data are of great importance for planning of health services, to evaluate the real needs for assistance and to study those factors that determine the transition from independence to loss of autonomy.

The Three-City Study (3C)

The main objective of the 3C Study is to estimate the risk of dementia attributable to vascular diseases or vascular risk factors and to provide data for modelling the expected impact of vascular risk reduction on the incidence and prevalence of dementia (<http://www.three-city-study.com/>). Other objectives are to study the incidence and risk factors of stroke, to provide data on the incidence and risk factors of coronary diseases, and to analyse temporal trends in the incidence and prevalence of incapacities and loss of autonomy (Alperovitch et al., 2002). Recruitment was undertaken based on the electoral registries of three French cities (Bordeaux, Dijon, and Montpellier) and included individuals aged 65 years and over between 1999 and 2011. The acceptance rate was 37% (9693) of the selected people who could be contacted.

Data were collected during face-to-face interviews using standardized questionnaires. Baseline work-up included extensive assessment of vascular risk factors, including blood pressure measurements, ultrasound examination of the carotid arteries, measurement of biological parameters such as blood glucose, urea and electrolytes, and lipids, cognitive functioning, and a clinical diagnosis of dementia. Cerebral MRI examinations were also performed in a sub-sample of 3442 persons aged between 65 and 79 years. Participants have been re-examined, on average, every 2 years. The third wave of follow-up examinations started in 2006 and was completed in 2012.

Dementia was diagnosed using a three-step procedure (3C Study Group, 2003). Firstly, screening was based on a thorough neuropsychological examination by trained psychologists. From the initial cohort of 9693 participants, seven had to be excluded as they were aged <65 years. Secondly, participants who were suspected of having dementia on the basis of their neuropsychological performance were examined by a neurologist. Four per cent of the participants refused to take part in the medical interview. Finally, all suspected dementia cases were analysed by a common independent committee of neurologists according to the DSM-IV criteria. The committee reviewed by teleconference all potential cases of dementia of the three study centres to obtain a consensus on the diagnosis and aetiology, based on all existing information. With regard to the different subtypes of dementia, AD was diagnosed according to the NINCDS-ADRDA criteria, and vascular dementia based on the history of vascular disease, the Hachinski score (Hachinski, 1994), and MRI whenever possible (Raffaitin et al., 2009). To date, the baseline vascular risk has been investigated and the prevalence of vascular disease at baseline explored (3C Study Group, 2003).

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3C: dementia

The baseline prevalence of dementia was 2.2% (3C Study Group, 2003). During 4 years of follow-up, 0.84 incident dementia cases per 100 person-years (95% CI = 0.72, 0.95) were validated (Raffaitin et al., 2009). The authors investigated the relationship between incident dementia and metabolic syndrome, defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria (Grundey et al., 2005). Metabolic syndrome was present in 15.8% of the study participants, and its presence increased the risk of incident vascular dementia, but not AD, over 4 years (Raffaitin et al., 2009). High triglyceride level was the only component of metabolic syndrome that was significantly associated with the incidence of all-cause (HR = 1.45, 95% CI = 1.05, 2.00) and vascular (HR = 2.27, 95% CI = 1.16, 4.42) dementia. Diabetes, but not impaired fasting glycaemia, was significantly associated with all-cause (HR = 1.58, 95% CI = 1.05, 2.38) and vascular (HR = 2.53, 95% CI = 1.15, 5.66) dementia. It is worth highlighting that one of the challenges in studies which use all the available information to diagnose subtypes of dementia is that it is difficult to avoid the circular process of diagnosis of vascular dementia, which might result in over-emphasizing the strength of relationships.

3C: depression

The relationship between metabolic syndrome and depression was also investigated. Both metabolic syndrome and depressive symptoms increased during old age (Akbaraly et al., 2011). Over the 4-year follow-up, 827 (18.6%) new cases of depression, measured using the CES-D Scale (Radloff, 1977), were observed. Participants with metabolic syndrome were more likely to develop depressive symptoms (OR = 1.73, 95% CI = 1.02, 2.95), compared to participants without metabolic syndrome, even after adjusting for socio-demographic characteristics, smoking, alcohol consumption, and health status factors such as treatment, cognitive deficit, disability, body mass index, and self-reported history of cardiovascular disease at baseline. However, this association was not significant within the older age groups (70–75, 75–80, and 80–91 years). Regarding the specific components of metabolic syndrome, low high-density lipoprotein (HDL) cholesterol was associated with increased odds of new-onset depressive symptoms in those aged 65–69 years. These results suggest that onset of late-life depression (age above 70 years) does not share the same aetiology and risk factors as onset of depressive symptoms in middle-aged and ‘young’ old people. However, the results could also be due to different response rates or bioresources at different ages.

3C: summary

This is a population-based study which focuses on the investigation of the association between vascular health, cerebrovascular disease, and risk of cognitive decline and dementias. New data collected from the third wave

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of follow-up has been important for investigating the long-term impact of vascular disease and its risk factors on cognitive health.

Epidemiological Clinicopathological Studies in Europe (EClipSE)

EClipSE harmonizes the neuropathological and longitudinal clinical data of brain donors from three population-based, prospective, longitudinal studies of ageing in Europe that included a brain donation programme: the CFAS (baseline 1989–1993), the CC75C (baseline 1985), and the Vantaa 85+ (baseline 1991) studies (EClipSE Collaborative Members, 2009) (<http://www.eclipsestudy.eu>). The project was created to address the lack of statistical power within individual studies for specific analyses assessing relationships between data collected during life and neuropathology at death. All three studies interviewed participants at regular intervals, including information on socio-demographic details and health status, in addition to cognitive function, including dementia diagnosis. Neuropathological parameters include neocortical and hippocampal neuritic plaques, diffuse plaques, tangles, cerebral amyloid angiopathy and atrophy, lacunes, infarcts, white matter pallor, Braak stage, and brain weight. This study is the largest data set of its type in the world, with brain donor sample sizes of 241 (CC75C), 304 (Vantaa 85+), and 548 (CFAS).

EClipSE: dementia

The potential protective role of education for dementia was explored within the EClipSE study (Brayne et al., 2010). Almost all older people have some pathology in their brain at death but have not necessarily died with dementia. The relationship between education and brain pathology at death was investigated, testing the hypothesis that greater exposure to education reduces the risk of dementia through either protection from pathology or compensatory mechanism (EClipSE Collaborative Members et al., 2010). Education during earlier life was recorded in number of years; incident dementia was detected through follow-up interviews, complemented by all the available sources of information such as retrospective informant interviews, death certificate data, and linked health/social records after death. Dementia-related neuropathologies were assessed, based on the CERAD protocol (Mirra et al., 1991). Eight hundred and seventy-two brain donors were included, of whom 56% were diagnosed as having dementia at death. The main findings in this study were that longer years in education were associated with decreased dementia risk at death (OR = 0.89, 95% CI = 0.83, 0.94). Moreover, education did not protect individuals from developing neurodegenerative and vascular neuropathology by the time they died, but it did appear to mitigate the impact of pathology on the clinical expression of dementia before death. In other words, for a specific pathological burden, those participants who remained in education for longer, earlier in life, were at reduced dementia risk in older age. These results support the ‘brain reserve hypothesis’ (Stern, 2002; Valenzuela, 2008) where greater exposure to education reduces the risk of clinical dementia by

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compensating for the pathological burden later in life, rather than being protective against the accumulation of pathology.

Geographical and cross-cultural differences such as education should be taken into account when interpreting the study results. During the early mid-twentieth century, the educational systems differed considerably between the UK (CFAS and CC75C) and Finland (Vantaa 85+). Participants from CFAS and CC75C completed an average of 9 years of formal education, while participants from the Vantaa 85+ study completed approximately 4 years. However, even after controlling the analysis regarding education and dementia for study site differences, age, and sex, the results remained strongly associated.

EClipSE also investigated the significance of rarer and 'disregarded' pathologies, such as Pick bodies, severe neuronal loss, gliosis, and granulovacuolar degeneration, along with brainstem plaques, tangles, neuronal loss, gliosis, pigmentary incontinence, and Lewy bodies, in relation to dementia in the population. A total of 627 individuals with clinical dementia were assessed. All pathologies were associated with dementia when controlling for plaques and tangles, except Hirano bodies, granulovacuolar degeneration, and brainstem plaques, which shows that dementia in old age is associated with a broad range of pathological and anatomical substrates (Keage et al., 2012).

EClipSE: depression

Depression has not yet been studied within the EClipSE data resource.

EClipSE: summary

The EClipSE study represents a unique resource of neuropathological and longitudinal clinical data of brain donors in Europe. Data from three studies were combined: CFAS in England and Wales, CC75C in England, and the Vantaa 85+ study in Finland. The finding that education can mitigate the impact of pathology on the clinical expression of dementia, combined with an understanding of life course factors, supports investments in health and education in early life.

Newcastle 85+ Study

The focus of the Newcastle 85+ Study is the oldest old. The main aim is to examine health trajectories and outcomes as the cohort ages and their associations with underlying biological, medical, and social factors. All individuals born in 1921 who were permanently registered with a participating general practice in Newcastle upon Tyne or North Tyneside primary care trusts in the UK were sampled (Collerton et al., 2007). Of the 1470 people eligible to participate, 1042 participated, with three having health assessment only, 188 having general practice record review only, and 851 having both (Collerton et al., 2009). Participants were re-seen at 18 (phase 1), 36 (phase 2), and 60 (phase 3) months. Since

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September 2016, the study has been undertaking a 10-year follow-up (phase 4).

For most diseases, prevalence was determined on the basis of a review of data from general practice records alone. The targeted common old age chronic diseases include: hypertension, ischaemic heart disease, cerebrovascular disease, peripheral vascular disease, heart failure, atrial flutter or fibrillation, arthritis, osteoporosis, chronic obstructive pulmonary disease or asthma, diabetes, hypothyroidism, hyperthyroidism, cancer diagnosed within the past 5 years, eye disease, dementia, Parkinson's disease, and renal impairment.

Newcastle 85+ Study: dementia

Screening for dementia was based on the standardized MMSE score (sMMSE). Using the sMMSE score, moderate or severe cognitive impairment was found in 12.5% (105/840) of participants, of whom 53% (56/105) had no diagnosis of dementia in their general practice records. Therefore, the prevalence of undiagnosed cognitive impairment was estimated at 7%.

Newcastle 85+ Study: depression

Depression was assessed using the GDS. Similar results were disclosed for depression as for dementia; 8.4% of the participants (65/772) had a GDS score suggestive of severe depression, of whom 82% (53/65) had no diagnosis recorded in their general practice records in the previous year.

Newcastle 85+ Study: summary

Overall, this large cohort of 85-year olds showed good levels of both self-rated health and functional ability, despite significant levels of disease and impairment. Hypertension, ischaemic heart disease, atrial fibrillation, depression, and dementia may, however, be underdiagnosed among this age group.

Conclusion

There is a continuous need for further epidemiological research in old age psychiatry as the world population is ageing. Neuropsychiatric conditions, such as depression and dementia, cognitive impairment, and behavioural and functional decline, place a considerable onus on health, social, and economic systems. Of particular importance is the potentially large impact on resources and care worldwide. Indeed, the cost of dementia is significant, not only in terms of personal cost, but also on societal resources. As highlighted in this chapter, many large population-based cohort studies have been undertaken in the ageing population, worldwide and in Europe, in order to better identify patterns of disease and disease risk factors.

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There is, however, no standardized approach to the diagnosis of dementia, cognitive dysfunction, and depression. As a result, estimates of disease prevalence and incidence that have been reported across studies may vary, not due to true differences, but as a result of methodology. Reported estimates could also vary across studies as a result of differences in the presence of risk and protective factors across individuals and as a result of cultural variation. Such variability is important to identify, especially for the development of preventative strategies (such as those linked to modifiable factors such as diet, educational exposure, and health-related comorbidity). Furthermore, the type of information collected and the method of assessment are variable across the studies. For example, some studies report cardiovascular disease comorbidity (self-reported or objectively measured), brain-related changes (determined through neuroimaging), psychiatric-related comorbidity (e.g. behavioural and psychological symptoms of dementia), blood-based biomarkers (including nutritional and genetic risk markers), or neuropathology. No single study has included all the measures required to completely map the full spectrum of risk/protective factors and the determinants of disease progression. Summarizing the results across all studies suggests that with the age demographic transition, the impact of dementia and age-related conditions is, and will continue to be, considerable. Better methodology for extracting and weighting data across studies will be important for future synthesis of cross-study analysis and for informing the design of new cohort studies focused on the life course of ageing populations.

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Neuropathology

Chapter: Neuropathology

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Introduction

This chapter mainly describes the neuropathological lesions of age-associated neurodegenerative diseases and their related pathological classifications to assist the reader in interpreting neuropathological reports. It is beyond the scope of this chapter to provide a comprehensive review of the neuropathology of all neurodegenerative diseases. Cerebrovascular disease, which is common and strongly age-associated, is covered and the chapter also reviews the increasing evidence on cerebral multimorbidity, i.e. the presence of multiple pathologies in post-mortem brains. It is now recognized that multimorbidity in the aged brain is the rule, while pure pathologies are the exception (Jellinger and Attems, 2015; Rahimi and Kovacs, 2014). Finally, we give a view on new and currently emerging neuropathological methods that should more accurately reflect the burden of pathology seen in post-mortem brains.

Neurodegeneration: general considerations

Neurodegenerative diseases are characterized by progressive neuronal dysfunction, with consecutive loss of specific populations of neurons that frequently involve distinct anatomically related systems (Jellinger, 2010). Thus, selective neuronal vulnerability is a characteristic feature of neurodegenerative diseases. It should be emphasized that diseases with known vascular, toxic, metabolic, infectious, or immunologically determined causes are, by definition, not classified as (primary) neurodegenerative diseases. The clinical presentation of neurodegenerative diseases depends on the system or region affected by the disease, rather than on the molecular nature of the characteristic neuropathological lesion per se, e.g. severe neuronal loss in the substantia nigra will clinically present as parkinsonism, irrespective of the associated neuropathological lesion, which potentially could be aggregates of α -synuclein (Lewy bodies), hyperphosphorylated tau (neurofibrillary tangles), cerebrovascular lesions, or other pathologies. Admittedly, the most likely neuropathological lesion associated with clinical parkinsonism is α -synuclein deposition in the substantia nigra, in which case the neuropathological diagnosis would be Lewy body disease with brainstem preponderance, i.e. Parkinson's disease (PD) (Dickson, 2018, Jellinger, 2014). On the other hand, in patients with advanced Alzheimer's disease (AD), the substantia nigra is often affected by tau pathology, resulting in clinical parkinsonism (Attems et al., 2007), and vascular lesions in the basal ganglia, thalamus, and substantia nigra are well recognized as causing vascular parkinsonism, which is a rare form of parkinsonism (Dickson, 2018).

What are the causes and mechanisms of neuronal dysfunction and cell death in neurodegeneration? Apoptosis, or 'programmed cell death', is an attractive mechanism to explain selective neuronal vulnerability (Dickson, 2011), while the term necrosis refers to the morphological changes that take place in a living organism in response to a noxious stimulus that causes cell death. In the CNS, necrosis is commonly observed after trauma, infection, and infarction, conditions that, by definition, do not fall into the category of neurodegeneration.

Apoptosis, on the other hand, is regulated by extrinsic (receptor-mediated) or intrinsic (mitochondria-mediated) pathways that, via the activation of caspases, lead to degradation of both DNA and cytoskeletal proteins. In several neurodegenerative diseases, damage resulting from reactive oxygen species has been identified as a major cytopathological feature, and cells that fail to compensate for oxidative stress enter apoptosis, suggesting that oxidative stress plays an important role in neurodegeneration (Jellinger, 2006; Jellinger, 2010). However, apoptosis leads to cell death within hours, while neurodegenerative diseases typically have a course of years, possibly due to an increased compensatory cellular response to neurodegeneration in living organisms. In addition, failure in the maintenance of mitochondria has been

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suggested to play a role in neurodegeneration (Karbowski and Neutzner, 2012).

While the respective roles of apoptosis, oxidative stress, and mitochondria in neurodegeneration remain unclear, aggregation of misfolded proteins (that might be neurotoxic) is a well-described and unifying feature of neurodegeneration. Various proteins, e.g. amyloid- β (A β) and tau, lose their native structure and form fibrils rich in β -sheets that accumulate intra- or extracellularly (Jellinger, 2010). Indeed, the nature of the respective misfolded protein, in conjunction with the topographical localization of the affected regions, is the basis for the classification of neurodegenerative diseases (Table 5.1).

Table 5.1 Major protein aggregates in neurodegenerative diseases.

Disease	Protein aggregate	Characteristic form	Localization
Alzheimer's disease	tau (3R, 4R)	NFT, NT	Neuronal cell bodies (NFT) and processes (NT)
	A β (1-40, 1-42)	A β plaque	Extracellular
	A β (1-40, 1-42) and tau (3R, 4R)	NP	A β , extracellular; tau, neuronal processes
Lewy body diseases			
<i>Parkinson's disease</i>	α -synuclein	LB, LN	Neuronal cell bodies (LB) and processes (LN)
<i>Dementia with Lewy bodies</i>	α -synuclein	LB, LN	Neuronal cell bodies (LB) and processes (LN)
Multiple system atrophy	α -synuclein	GCI	Cytoplasm of glial cells

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Frontotemporal lobar degeneration			
<i>Pick's disease</i>	tau (3R)	Pick bodies	Neuronal cell bodies
<i>Corticobasal degeneration</i>	tau (4R)	Astrocytic plaque	Distal segments of astrocytes
<i>Progressive supranuclear palsy</i>	tau (4R)	Globose NFT	Neuronal cell bodies
	tau (4R)	Tufted astrocyte	Astrocytic cell bodies
<i>Agyrophilic grain disease</i>	tau (4R)	Grains	Neuronal processes (dendrites)
<i>Neurofibrillary tangle dominant dementia</i>	tau (3R, 4R)	NFT, NT	Neuronal cell bodies (NFT) and processes (NT)
<i>FTLD-TDP</i>	TDP-43	NCI (NII)	Neuronal cytoplasm (and nuclei)
<i>FTLD-UPS</i>	Ubiquitin	NCI (NII)	Neuronal cytoplasm (and nuclei)
<i>FTLD-FUS</i>	FUS protein	NCI (NII)	Neuronal cytoplasm (and nuclei)
<i>FTLD-ni</i>	none known	n.a.	n.a.

3R, 3-repeat tau; 4R, 4-repeat tau; NFT, neurofibrillary tangle; NT, neuropil thread; LB, Lewy body; LN, Lewy neurite; NCI, neuronal cytoplasmic inclusion; NII, neuronal intranuclear inclusions.

For various forms of FTLD, see main text.

Despite considerable advances in our understanding of some pathomechanisms that ultimately lead to sporadic age-associated neurodegeneration, the exact causes for protein accumulation await

further elucidation and are likely to be multifactorial. However, in hereditary neurodegenerative diseases, the mechanisms that cause accumulation of misfolded proteins are, in most cases, reasonably well understood, thereby providing helpful information to further our understanding of patho-mechanisms in sporadic neurodegeneration; for example, in trisomy 21 (Down's syndrome), an increased expression of the amyloid precursor protein (APP) that is encoded on chromosome 21 leads to an increased production of A β , with consequent formation of A β plaques. However, another possibility for the increased production of A β in both sporadic and hereditary (e.g. mutations in presenilin genes 1 and 2) neurodegenerative diseases and ageing might be an increased activity of β - and γ -secretase, which leads to an increased formation of A β oligomers (for more details on amyloid processing, see Alzheimer's disease, p. 79).

On the other hand, a decrease in protein degradation and/or elimination out of the brain may cause protein accumulation and aggregation; cellular protein degradation and clearance are mediated via both the ubiquitin-proteasome system (UPS; ubiquitin pathway) and the autophagy-lysosomal pathway (ALP). Failure of UPS and ALP might be caused by increasing amounts of proteins that overwhelm these systems and/or malfunction of the systems themselves, both probably resulting in protein misfolding and aggregation (Jellinger, 2010). Similarly, reduced elimination out of the brain could lead to accumulation of the respective protein; in the CNS, solutes are mainly transported out of the brain via drainage along the perivascular pathway, and impairment of the perivascular pathway has been suggested to result in A β accumulation (Weller et al., 2009).

It is generally assumed that misfolded proteins exert neurotoxicity, but the underlying mechanisms are poorly understood. Misfolded proteins form soluble oligomers that aggregate into insoluble structures, and by using appropriate histochemical techniques and immunohistochemical antibodies, these insoluble structures can be seen on microscopic examination. However, it is not clear if the soluble oligomers and/or the insoluble, microscopically visible aggregates are the neurotoxic species. This has important implications with respect to the interpretation of neuropathological findings regarding disease mechanisms, as neuropathology detects insoluble aggregated proteins, but not the soluble oligomers. It has indeed been suggested that the formation of insoluble aggregates represents a protective mechanism, insofar as neurotoxic oligomers are 'trapped' in their aggregated form and thereby lose their neurotoxic property. Alternatively, the accumulation and aggregation of proteins might primarily be the result of synaptic and/or cellular damage, rather than the cause for cell death (Jellinger, 2010).

It was believed previously that protein aggregate formation is an entirely cell-autonomous process occurring independently in many cells. However, it is now thought that a prion-like mechanism is responsible for the spread of misfolded proteins (e.g. tau and α -synuclein) throughout the

brain (Goedert et al., 2014). This does not imply that age-associated neurodegenerative diseases are prion diseases, as the latter are characterized by an infective agent, i.e. the prion protein (see Prion diseases, p. 89). Such prion-like mechanisms rather implies that a limited number of neurons initially develop misfolded proteins which can then induce misfolding of the corresponding physiological protein in neighbouring neurons. This has huge therapeutic implications, as novel strategies aiming to prevent prion-like spread are currently being developed.

In most age-associated neurodegenerative diseases, the amount of pathology is crucial for the development of clinical symptoms. In particular, AD pathology is frequently present to a limited extent in the brain of many people without dementia (Jack et al., 2014; Jellinger and Attems, 2012; Mufson et al., 2016). It is therefore still a matter of discussion whether age-associated neurodegenerative diseases are a pure consequence of ageing, rather than a distinct disease, or if age is an important risk factor but would not inevitably lead to the development of full-blown disease with overt clinical symptoms, even in individuals aged over 100 years.

Neurodegeneration per se usually does not lead to fatal brain lesions that would cause the death of a patient but naturally can be considered as a severe underlying disease that predisposes individuals to acquire potentially fatal diseases. Bronchopneumonia most frequently represents the immediate cause of death in AD (approximately 50%), while in patients with vascular dementia (VaD), cardiovascular disease has been shown to be the immediate cause of death in approximately 50% (Attems et al., 2005b).

Alzheimer's disease

AD is the most frequent neurodegenerative disease, accounting for 50–80% of dementias. Both prevalence and incidence increase with age; in 65- to 69-year olds, the prevalence is 1%, doubling with each subsequent 5-year increment. Above the age of 85 years, prevalence rates range from 20% to 50%. Therefore, increasing age is the most important risk factor for AD (see Chapter 30 for details and other risk factors).

The neuropathological diagnosis of AD is based on the semi-quantitative and topographical assessment of A β plaques, neurofibrillary tangles/neuropil threads (NFTs/NTs), and neuritic plaques (NPs). However, additional neuropathological lesions, such as cerebral amyloid angiopathy (CAA) and granulovacuolar degeneration (GVD), are typically present, but assessment of those lesions is not required for stating a neuropathological diagnosis, according to current diagnostic criteria. The loss of neurons (Gomez-Isla et al., 1996) and synapses (Terry et al., 1991) in AD has been shown to be more directly related to the severity of the cognitive deficit. Using quantitative methods in human brain tissue of AD and controls, the correlation between neuronal loss, NFTs, and cell death

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markers has been studied recently and the findings suggest that caspases and changes in macroautophagy play a role early in the disease (Theofilas et al., 2018).

Neuropathology of AD

On gross examination, post-mortem brains of AD patients often appear relatively normal, without striking pathological changes, and reduction in brain weight may be minimal. However, if present, the characteristic atrophy in AD involves the entorhinal cortex, hippocampus, amygdala, and olfactory bulb, as well as the inferior temporal, superior frontal, and middle frontal gyri (Fig. 5.1). In all of these areas, tau pathology predominates and atrophy in AD is not associated with the burden of A β plaques (Josephs et al., 2008). Cerebral atrophy leads to enlargement of the ventricles (i.e. *hydrocephalus internus e vacuo*) and the cortical ribbon may be thin. The substantia nigra is well pigmented, while the locus caeruleus might be pale and the cerebellum is normal.

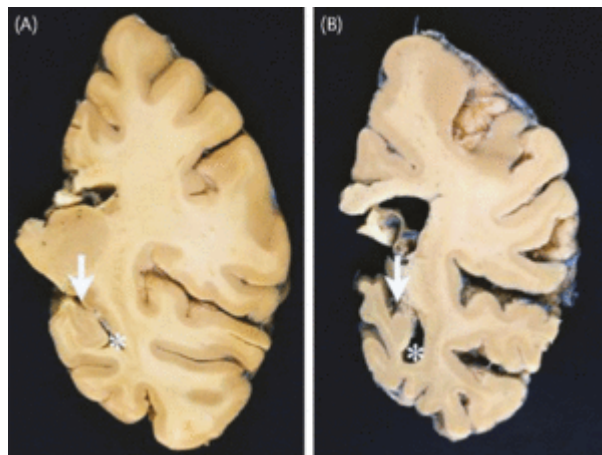


Fig. 5.1

Comparison between formalin-fixed brain slices of the left hemispheres (level of posterior hippocampus) of an aged nondemented individual (A) and an AD patient (B). Note the marked atrophy (thinning of the gyri and deepening of the sulci) in B, in particular hippocampal atrophy (arrow in B) with widening of the inferior horn of the second ventricle (asterisk in B).

Reproduced courtesy of Simon Fraser and Arthur Oakley.

In AD, neuronal loss has been described, in particular in the nucleus basalis of Meynert, the amygdala, the olfactory bulb with the olfactory nucleus, the locus caeruleus, and the serotonergic raphe nuclei. Another important feature of AD is synaptic loss and there is strong evidence that synapses play a major pathophysiological role in AD (Duyckaerts et al., 2009). Band-like spongiosis and reactive astrogliosis may be present in AD. Despite the fact that the aforementioned lesions are of

pathophysiological importance for AD (neuronal and synaptic loss) or frequent findings (spongiosis), they are not used for neuropathological diagnostic purposes, which rely on the assessment of NFTs/NTs and A β plaques, including NPs.

Neurofibrillary tangles and neuropil threads

NFTs and NTs are aggregates of hyperphosphorylated microtubule-associated protein (MAP) tau. MAP tau is particularly abundant in axons, and its physiological function is primarily to stabilize microtubules. Six isoforms of MAP tau exist in the human brain and, based on the number of C-terminal microtubule-binding repeat motifs, 3-repeat (3R) and 4-repeat (4R) isoforms can be distinguished (Mandelkow and Mandelkow, 2012). In the dephosphorylated state, MAP tau binds to microtubules, while phosphorylation leads to detachment from microtubules. Under physiological conditions, MAP tau is in a dynamic equilibrium, on and off the microtubules, but under pathological conditions (neurodegeneration), MAP tau is hyperphosphorylated, resulting in the disintegration of microtubules and the aggregation of insoluble filaments/fibrils composed of hyperphosphorylated MAP tau (Ballatore et al., 2007). NFTs/NTs are composed of aggregates of hyperphosphorylated MAP tau, while so-called pre-tangles represent non-aggregated hyperphosphorylated or abnormally phosphorylated MAP tau and are considered to be precursors of NFTs/NTs. Importantly, the extent of NFTs/NTs in the neocortex has been shown to correlate with cognitive deficits (Nelson et al., 2012).

Using appropriate immunohistochemical antibodies (e.g. AT8), both NFTs and NTs can be visualized for histological assessment (Fig. 5.2). Of note, in AD, both 3R and 4R tau isoforms are present, while some tauopathies are characterized by the exclusive presence of either 3R or 4R tau (for details, see Frontotemporal lobar degenerations (including tauopathies, p. 86). NFTs are located in neuronal cell bodies, and NTs in axons and dendrites, with the latter appearing in immunohistochemically stained sections as immunopositive threads in the neuropil (i.e. area of unmyelinated axons, dendrites, and glial cell processes, practically the area between cell bodies). It has been suggested that the amount of NTs, rather than NFTs, should be assessed for diagnostic purposes (Alafuzoff et al., 2008). NFTs and NTs are predominately found in the hippocampus, the entorhinal cortex, and layers III and VI of the isocortex. However, NFTs and NTs are also present in the olfactory bulb and subcortical nuclei, in particular the locus caeruleus, in early preclinical stages of AD (Attems et al., 2012; Braak et al., 2011).

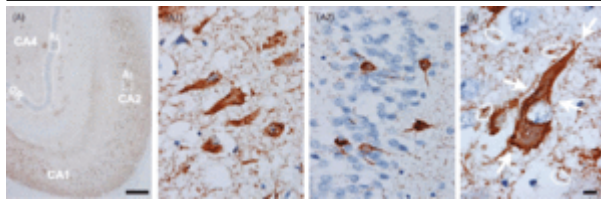


Fig. 5.2

In AD, high amounts of neurofibrillary tangles and neuropil threads are seen in the hippocampus (A), among other regions (see main text). Arrows in B mark a neuronal cell body that comprises a neurofibrillary tangle, while ovals encircle some of the many neuropil threads in neuronal processes that are seen in this photomicrograph. CA1, CA2, and CA4 hippocampal *cornu ammonis* (Ammon's horn) sectors 1, 2, and 3, respectively; GR, granule cell layer of the dentate gyrus. Immunohistochemistry with antibody against hyperphosphorylated tau AT8.

Scale bars: A, 50 μm ; B, 10 μm .

It is generally assumed that in AD, NFTs and NTs primarily manifest in transentorhinal and entorhinal cortices and then gradually spread towards the hippocampus and isocortex (Braak and Braak, 1991), and this pattern is the basis for the diagnostic Braak stages (see Neuropathological diagnostic criteria for AD, p. 82). However, pre-tangle material (i.e. hyperphosphorylated, but non-aggregated, tau) was found in the locus caeruleus in the majority of individuals under 30 years of age who were devoid of cortical tau pathology, suggesting that tau pathology begins in the locus caeruleus, rather than the transentorhinal cortex (Braak et al., 2011), but this is controversial (Attems et al., 2012).

Amyloid- β plaques

A β peptides (4 kDa) are generated by β - and γ -secretase cleavage of the transmembranous APP and comprise peptides terminating at carboxyl terminus 40 (A β_{40}) and 42 (A β_{42}). Cerebral A β depositions are a hallmark of AD, but in the majority of clinicopathological correlative studies, cerebral A β load does not correlate with clinical dementia (Nelson et al., 2012). Nevertheless, most therapeutic approaches against AD target A β . This is mainly due to the so-called amyloid cascade hypothesis that postulates that an increase in A β is the trigger for a series of events that ultimately lead to the formation of NFTs/NTs (Hardy and Selkoe, 2002). The observation that mutations in genes that lead to an increase in A β (APP, presenilins) cause familial AD with tau pathology (NFTs/NTs), while mutations that lead to tau pathology cause familial tauopathies without A β , argues in favour of the 'amyloid cascade hypothesis'. However, several observations suggest that the 'amyloid hypothesis' might not apply for sporadic, age-associated AD; in the early stages of AD, A β is mainly present in neocortical areas, while tau pathology is seen in the

transentorhinal cortex, and it is not clear how A β influences tau at this distance. Furthermore, a large autopsy study analysing the prevalence of A β and tau pathology, as a function of age, demonstrated that tau pathology precedes A β (Tsartsalis et al., 2017). Also, APP transgenic mice develop abundant A β , but no tau pathology (Duyckaerts et al., 2009). However, the frequent co-occurrence of A β and tau, as well as the finding that the highest NT Braak stages V/VI (see Neuropathological diagnostic criteria for AD, p. 82) are never seen in the absence of A β , strongly suggests a mutual interaction between A β and tau (Spires-Jones et al., 2017). Although both A β and tau have been extensively studied with regard to their separate mode of toxicity, their possible interactions and synergistic effects in AD, linking A β and tau, are currently being investigated (Ittner and Gotz, 2010; Spires-Jones et al., 2017).

While A β ₄₀ constitutes the majority of cerebral A β (over 95%), A β ₄₂ is more aggregatable and hence believed to initiate the formation of oligomers, fibrils, and plaques (Masters and Beyreuther, 2011). A β aggregates extracellularly and, using appropriate antibodies (e.g. 4G8 antibody), various morphological forms of A β aggregates can be detected (Fig. 5.3). The main parenchymal A β deposits are diffuse or focal. Diffuse A β deposits are usually large (up to several 100 μ m) and show ill-defined borders; they are referred to as 'lake-like', 'fleecy', and 'subpial band-like'. A β plaques, on the other hand, are focal A β deposits; 'mature', 'classical', and 'neuritic' plaques can be distinguished.

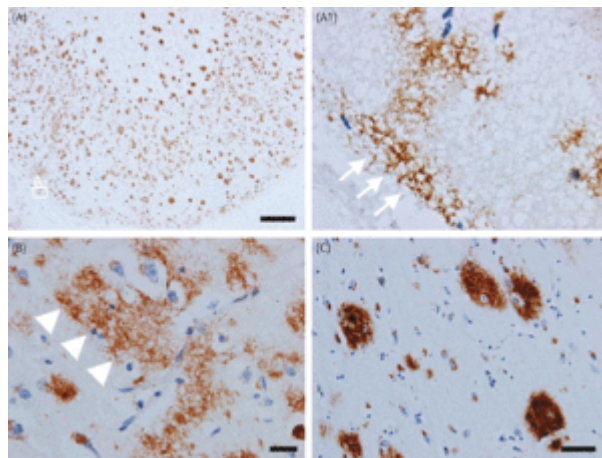


Fig. 5.3

A β depositions in the neocortex (A–C) show different morphology: subpial band-like A β (arrows in A1), fleecy A β (arrowheads in B), and A β plaques (C). Immunohistochemistry with A β antibody 4G8.

Scale bars: A, 500 μ m; B, 20 μ m; C, 50 μ m.

It should be emphasized that NPs contain—in addition to A β aggregates—hyperphosphorylated tau in dystrophic neurites (Fig. 5.4). NPs are strongly associated with AD, while other forms of parenchymal A β

deposits are frequently seen to a considerable extent in post-mortem brains of individuals without dementia (Jellinger and Attems, 2012) and, as mentioned earlier, their density does not correlate with clinical dementia (Duyckaerts and Dickson, 2011). However, it has been suggested that the most advanced spread of A β —Thal A β phases 4 and 5—is correlated with clinical dementia (see Neuropathological diagnostic criteria for AD, p. 82). According to recent *in vivo* ^{18}F -AV-1451 PET imaging and post-mortem studies, tau pathology is related in a degeneration-specific manner to cognitive impairment in AD, which is weakly related to amyloid burden, but, in part, mediated by grey matter volume (Bejanin et al., 2017).

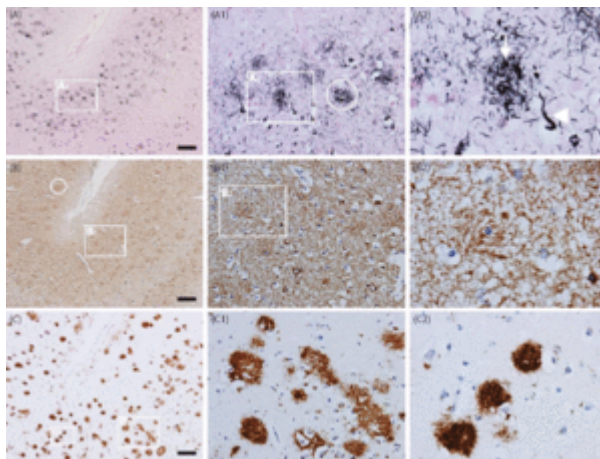


Fig. 5.4

Neuritic plaques are a neuropathological hallmark lesion of AD and represent A β plaques that contain tau in distended neuronal processes (i.e. dystrophic neurites). A–C are photomicrographs from adjacent histological sections. A, Gallyas silver stain visualizes both aggregated A β and tau and is therefore ideal to detect neuritic plaques (ring in A1, neuritic plaque; arrow in A2, dystrophic neurite; arrowhead in A2, neurofibrillary tangle). On the other hand, the combined use of tau (B, antibody AT8) and A β (C, antibody 4G8) immunohistochemistry on adjacent sections is also useful to detect neuritic plaques, as tau immunopositivity shows a plaque-like pattern (ring in B) and A β immunostaining confirms the presence of A β plaques (C).

Scale bars: A, B, and C, 200 μm .

Additional lesions in AD

Although the neuropathological diagnosis of AD solely relies on the assessment of both A β and tau pathology, a variety of additional neuropathological lesions are usually present. Indeed, the presence of multiple pathologies in the brain of older people with and without dementia is not an exceptional finding, and this is addressed in detail in

Cerebral multimorbidity, p. 91. However, there are some additional pathologies that are particularly frequent in AD; among those are CAA, cerebrovascular lesions, hippocampal sclerosis, transactivation-responsive DNA-binding protein 43 (TDP-43) pathology, and GVD. Although GVD may be present in diseases other than AD, it is regarded as a primarily AD-related phenomenon and therefore is described in the next section, while TDP-43 pathology in AD is described in Cerebral multimorbidity, p. 91 and other additional pathologies in their own respective sections.

Granulovacuolar degeneration

The term GVD describes vacuolar changes in the cytoplasm of neurons of the medial temporal lobe, in particular in pyramidal neurons of the hippocampus, often in association with NFTs, but they have also been described in other regions (e.g. neocortex, amygdala). GVD has been reported to be more frequent in AD, compared to controls, and may be present in tauopathies (e.g. Pick's disease, progressive supranuclear palsy). GVD first develops in neurons of the CA1/CA2 hippocampal subfield and then expands in a predictable sequence into other brain regions, allowing for the distinction in five different stages (Thal et al., 2011). Importantly, these stages are related to AD pathology, pointing towards a role of GVD in AD pathogenesis.

White matter lesions in AD

White matter lesions (WMLs) histologically encompass structural damage of the cerebral white matter as a result of white matter rarefaction, are visualized as white matter hyperintensities (WMHs) on *pre-* and *post-mortem* T2-weighted MRI, and have been associated with a wide range of cognitive deficits (McAleese et al., 2016). The pathogenesis of WMHs is generally thought to be associated with small vessel disease (SVD), but recent studies have suggested a multifactorial aetiology of WMHs, inclusive of SVD-related ischaemia, but also degenerative axonal loss secondary to cortical AD pathology (McAleese et al., 2017b). Indeed, it appears that in neurodegenerative diseases, such as AD, WMHs, in particular in the parietal lobe, are likely to be primarily associated with cortical tau pathology, and hence WMHs on MRI images from individuals with dementia should be considered to represent a surrogate marker for severe cortical tau pathology, thus supporting a clinical diagnosis of AD, rather than suggesting the presence of significant vascular disease.

Neuropathological diagnostic criteria for AD

With the progression of the disease, the major neuropathological lesions of AD progress stepwise, following a hierarchical pattern:

1. Braak neurofibrillary stages describe the progression of NFTs/NTs from the transentorhinal and entorhinal areas (stages I and II) to the hippocampus (stage III), the temporal cortex (stage IV), and finally other neocortical areas, of which the occipital cortex (stages V and

VI) is used for staging purposes (Braak and Braak, 1991; Braak et al., 2006).

2. Thal A β phases describe the progression of parenchymal A β depositions; in phase 1, the isocortex is involved, the hippocampus and entorhinal cortex in phase 2, the striatum and diencephalic nuclei in phase 3, the brainstem nuclei in phase 4, and finally the cerebellum and additional brainstem nuclei in phase 5; phases 4 and 5 are suggested to be correlated with clinical dementia (Thal et al., 2002b).

Several criteria for the neuropathological diagnosis of AD are in use:

- Age-adjusted criteria of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) are based on the semi-quantitative assessment of NPs (sparse, moderate, frequent) in the middle frontal gyrus, superior/middle temporal gyri, and inferior parietal lobule (Mirra et al., 1993).
- The National Institute of Aging Nancy and Ronald Reagan Institute (NIA-RI) criteria give the probability that a clinical dementia has been caused by AD and are based on both CERAD criteria and Braak neurofibrillary stages, i.e. CERAD neg. and Braak neg.—no probability; CERAD A and Braak I/II—low probability; CERAD B and Braak III/IV—medium probability; and CERAD C and Braak V/VI—high probability (Hyman, 1998).
- The most commonly used criteria are the NIA-Alzheimer's Association guidelines that combine Thal A β phases, Braak neurofibrillary stages, and the CERAD criteria (Montine et al., 2012). According to these guidelines, a neuropathological report should state the A β plaque score (Thal et al., 2002b), Braak neurofibrillary stage (Braak et al., 2006), and CERAD NP score (Mirra et al., 1993), which yield a combined 'ABC score' (Montine et al., 2012). This ABC (amyloid, Braak, CERAD) score should be stated, regardless of clinical history, to reflect the amount of 'Alzheimer's disease neuropathologic change'. Table 5.2 illustrates how each A, B, and C score is determined and transformed to state the level of AD neuropathological change on a four-tiered scale: 'not', 'low', 'intermediate', and 'high'.

Neuropathology

Table 5.2 ABC criteria for the diagnosis of Alzheimer's disease-related pathology.

Level of AD neuropathologic change						
<i>Thal phase for Aβ plaques</i>	A	B			C	CERAD
		0 or 1	2	3		
0	0	Not	Not	Not	0	neg
1 or 2	1	Low	Low	Low	0 or 1	neg or A
1 or 2	1	Low	Intermediate	Intermediate	2 or 3	B or C
3	2	Low	Intermediate	Intermediate	any C	neg or A to C
4 or 5	3	Low	Intermediate	Intermediate	0 or 1	neg or A
4 or 5	3	Low	Intermediate	High	2 or 3	B or C
		<i>Braak 0-II</i>	<i>Braak III-IV</i>	<i>Braak V-VI</i>		

The level of Alzheimer's disease (AD) neuropathologic change is determined by assessing A, B, and C scores. A scores are related to Thal phase for Aβ plaques (first column), B scores to neuritic Braak stages (bottom row), and C scores to CERAD stages (last column).

Adapted with permission from Montine, T. J., et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: A practical approach. *Acta Neuropathologica*, 123(1), 1-11. Copyright © 2011, Springer-Verlag. <https://doi.org/10.1007/s00401-011-0910-3>.

Cerebral amyloid angiopathy

CAA is defined as the deposition of congophilic material (i.e. positive staining with the Congo red dye) in cerebral leptomeningeal and intracortical arteries, arterioles, capillaries, and, rarely, veins. CAA is also referred to as congophilic amyloid angiopathy (Attems et al., 2011). CAA occurs in both hereditary or familial and sporadic forms. While the amyloid in sporadic, age-associated forms is predominately composed of A β , the nature of amyloid depositions in hereditary forms is determined by the respective underlying mutation (e.g. A-Bri and cystatin C in BRI2 and cystatin C gene mutations, respectively). Sporadic CAA is frequently, but not invariably, present in AD and is often observed in older individuals without AD (Attems and Jellinger, 2014). CAA is considered a risk factor for non-traumatic intracerebral lobar haemorrhage (ICH) in the elderly and is present in 5–20% of all cases with ICH (Pezzini et al., 2009), but in large autopsy cohorts, the prevalence of ICH in CAA cases was approximately 5%, being similar to cases without CAA (Attems et al., 2008). CAA may cause microbleeds (Greenberg et al., 2009) and, in moderate to severe stages, has been shown to be an independent risk factor for cognitive impairment (Matthews et al., 2009).

Histopathology of CAA

A β is initially deposited in the outer parts of the vessel wall, but with increasing severity, all layers of the vessel wall show A β depositions, accompanied by a loss of smooth muscle cells. In very severe stages of CAA, the vascular architecture is disrupted, but endothelial cells are usually preserved (Fig. 5.5).

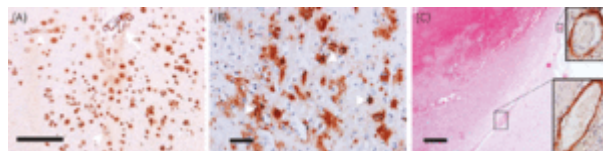


Fig. 5.5

Cerebral amyloid angiopathy (CAA) presents as A β depositions in the walls of meningeal (arrows in A) and cortical (arrowheads in A) arteries, while capillary CAA refers to A β depositions in the walls of capillaries (arrowheads in B). CAA may be the cause for nontraumatic intracerebral haemorrhage (ICH). Photomicrograph C shows an ICH (left upper part) in a patient with CAA; insets in C show photomicrographs of sections of the same block stained with anti-A β antibody 4G8, demonstrating CAA in regions adjacent to the ICH, thereby suggesting that CAA might have been the cause for ICH in this case. A and B and insets in C, 4G8 immunohistochemistry; C, H/E.

Scale bars: A and C, 500 μ m; B, 50 μ m.

CAA may frequently show a patchy distribution and primarily affects leptomeningeal and cortical vessels of neocortical regions. The occipital lobe has been reported to be the site that is both most frequently and severely affected by CAA, followed by either frontal, temporal, or parietal lobes (Attems et al., 2005a).

A β depositions in the walls of capillaries are referred to as capillary CAA (capCAA) and usually present as strong staining lining capillary walls in sections stained with appropriate A β antibodies. The presence of capCAA distinguishes two types of CAA—CAA-type 1 is characterized by the presence of capCAA and may show additional A β depositions in non-capillary blood vessels, whereas in CAA-type 2, A β depositions are restricted to leptomeningeal and cortical arteries, arterioles, and, rarely, veins without capillary involvement (Thal et al., 2002a). Of note, the frequency of the APOE ϵ 4 allele in CAA-type 1 is more than four times higher than in CAA-type 2 (Thal et al., 2002a). It has been shown recently that the presence of capCAA identifies a subtype of sporadic AD that is defined by characteristic neuropathological features and genotype-specific associations (Thal et al., 2010). Pericapillary A β deposits are predominately composed of A β ₄₂ and are clustered in the glia limitans around capillaries and represent another type of capillary involvement (Attems and Jellinger, 2004).

As of today, no standardized neuropathological consensus criteria for the scoring of CAA have been established, but several methods have been published and are usually used to describe the severity of CAA in post-mortem brains (Attems et al., 2011; Love et al., 2014).

Primary age-related tauopathy

NT pathology is not exclusively found in association with A β deposition, as evidenced by the disease primary age-related tauopathy (PART). PART is characterized by the presence of tau pathology in the form of NFTs and NTs without (definite PART) or with only limited (possible PART) parenchymal A β depositions up to Thal A β phase 2 (Crary et al., 2014). In addition, any other primary tauopathy has to be excluded. PART is frequent in old age (up to 40%) and is likely to represent the neuropathological correlate of a clinical condition termed ‘suspected non-AD pathophysiology’ (SNAP), which refers to individuals with temporal lobe atrophy on MRI and high CSF tau, but no evidence for cerebral A β depositions (Jack, 2014). SNAP is usually seen in cognitively normal elderly but may also be present in mildly impaired individuals. While the neuroanatomical progression of NFTs/NTs in PART follows AD-associated NFT Braak stages, the latter do not exceed stage IV in PART and NFT Braak stages V/VI are indeed only seen in the presence of A β pathology.

The relationship between PART and AD has been controversial; PART does not differ from AD-associated tau pathology, and one can argue that it actually represents an early stage of AD. However, the occurrence of ‘definite PART’ in many aged individuals clearly indicates that A β is not

necessary for the development of tau pathology, while high Braak stages V/VI, as seen in full-blown symptomatic AD, do not occur in the absence of A β . PART may therefore be considered as a distinct pathology, which is one of the prerequisites for the development of AD, but does not inevitably lead to AD (Jellinger et al., 2015). PART with clinical features of cognitive impairment may also be termed neurofibrillary tangle dominant dementia (NFTD). NFTD is characterized by the presence of NFTs/NTs that contain both 3R and 4R tau, while A β pathology is, in 80% of cases, completely absent or present to a very limited degree. Importantly, in NFTD, tau pathology is mostly confined to allocortical regions, corresponding to neurofibrillary Braak stage III, and rarely mild isocortical involvement is seen. NFTD accounts for 5–7% of late-onset dementias and differs from AD by a later onset (80 years), a shorter duration (5 years), less severe cognitive impairment, and almost absence of the *APOE ϵ 4* genotype (Jellinger and Attems, 2007a). Recent studies showed the absence of soluble A β with the tau gene *MAPT H1* haplotype, classifying it as a specific tauopathy independent of amyloid (Santa-Maria et al., 2012).

Hippocampal sclerosis

Hippocampal sclerosis (HS) is defined as severe astrogliosis and neuronal loss in the CA1 region of the hippocampus, where neurons are particularly vulnerable to hypoxia, and in the subiculum. HS occurs in up to 26% of older individuals, frequently as an additional finding in AD, and is often accompanied by multiple small infarcts in other brain regions and/or leukoencephalopathy (Jellinger, 2007a). It has been shown that patients with HS are older than those without HS and had more coronary artery disease, suggesting that related occult hypoxic-ischaemic episodes may represent pathogenic factors. On the other hand, TDP-43 pathology was detected in up to 70% of cases with HS, and approximately 50% of frontotemporal lobar degeneration-TDP (see FTLT with TDP-43 pathology, p. 88) cases show HS (Amador-Ortiz et al., 2007). In an autopsy study, TDP-43 pathology was seen in 18% of cases with HS, and in 42% of cases with concomitant AD pathology (Rauramaa et al., 2011). However, a causal link between HS and TDP-43 has not been demonstrated and their frequent co-occurrence might rather reflect a mere coincidence of two relatively common pathologies (Davidson et al., 2011). It has been suggested that HS may incorporate different subtypes: HS with advanced age (HS-ageing), with seizures (HS-SZ), with tauopathies (HS-tau), with non-tauopathy frontotemporal dementia (HS-FTD), and with cerebrovascular diseases (HS-CVD); HS-ageing is an important, but under-appreciated, brain disease of ageing (Nelson et al., 2013).

Ageing-related tau astrogliopathy

Ageing-related tau astrogliopathy (ARTAG) refers to pathological accumulation of tau in astrocytes, which show a thorn-shaped morphology, and may often be seen in clusters in grey and white matter, frequently surrounding blood vessels (Kovacs et al., 2016). ARTAG occurs

mainly, but not exclusively, in individuals over 60 years of age and has not yet been associated with a distinct clinical phenotype. Nevertheless, ARTAG is a frequent incidental finding in post-mortem brains, and its role in the spectrum of age-associated neurodegeneration is currently under investigation.

Lewy body diseases

Lewy body diseases (LBD) comprise PD, dementia with Lewy bodies (DLB), and Parkinson's disease dementia (PDD) (McKeith et al., 2017). In large autopsy series of patients with ante-mortem diagnosis of parkinsonism, the most common finding was DLB (77–84%), but only 34.8–44.7% were idiopathic PD (Dickson, 2018; Jellinger, 2007b). The characteristic neuropathological lesions of LBDs are Lewy bodies (LBs) in neuronal somata and Lewy neurites (LNs) in nerve cell processes. LBs and LNs are composed of α -synuclein aggregates. α -synuclein is a 140-amino acid residue protein that is a member of a family of proteins that include β - and γ -synucleins with unknown physiological function(s). α -synuclein is a lipid-binding protein (Goedert, 2001) located at presynaptic terminals in proximity to synaptic vesicles, and it has been suggested that its physiological function involves the modulation of synaptic transmission and neuronal plasticity (Waxman and Giasson, 2009). In addition, α -synuclein might be a chaperone protein, an inhibitor of phospholipase D2, and an active participant in oxidative stress production, as well as being both neuroprotective and neurotoxic (Spillantini, 2011). Under pathological conditions, phosphorylation of α -synuclein is enhanced (at serine 129), and its aggregates are the main component of LBs and LNs that may, in addition, contain ubiquitin and α -B-crystallin, among other proteins (Kalia and Kalia, 2015).

LBs occur in two types (Fig. 5.6): (1) classical LBs are spherical cytoplasmic inclusions, 8–30 μ m in diameter, with a hyaline eosinophilic core, concentric lamellar bands, and a narrow, pale-stained halo, that are predominately seen in pigmented neurons of the substantia nigra, locus caeruleus, and dorsal motor nucleus of the vagus nerve; and (2) cortical LBs are eosinophilic, rounded, angular, or reniform structures without a halo, which are seen in iso- and allocortical areas. Of note, while classical LBs can be easily detected on routine haematoxylin and eosin (H/E)-stained sections, cortical LBs are not readily detected, and immunohistochemistry for α -synuclein should be used to detect cortical LBs and LNs, the latter appearing as thin, immunopositive threads in the neuropil (Jellinger, 2014).

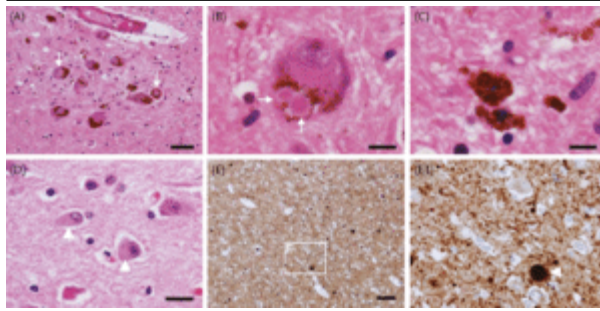


Fig. 5.6

Classical Lewy bodies in the substantia nigra (arrows in A and B) show a hyaline eosinophilic core and a narrow pale stained halo (B shows two Lewy bodies in one pigmented neuron). Degenerating pigmented neurons lose melanin (pigment incontinence) that may be incorporated by macrophages (C). On H/E sections, cortical Lewy bodies are rounded eosinophilic inclusions (D) in neuronal cell bodies that are readily detected with α -synuclein immunohistochemistry (E, arrowhead in E1) that also stains Lewy neurites as thread- and dot-like structures in the neuropil (E). A–D, H/E; E, α -synuclein immunohistochemistry.

Scale bars: A, 50 μ m; B–D, 20 μ m; E, 200 μ m.

Parkinson's disease

PD is one of the most frequent neurodegenerative movement disorders, with a mean age of onset of between 55 and 65 years. The prevalence in the general population is estimated at 0.3%, but this increases with increasing age to 3% in those over 65 years. The four cardinal clinical features are tremor at rest, rigidity, akinesia (or bradykinesia), and postural instability (TRAP), often associated with gait disturbances and falls (Jankovic, 2008). However, PD can present with a variety of additional clinical features, and various clinical subtypes have been described and the neuropathology underlying clinical variability in α -synucleinopathies (e.g. PD) has been described (Halliday et al., 2011).

On macroscopic examination, the most remarkable feature of PD is pallor of the substantia nigra and often the locus caeruleus. Histologically, abundant LBs and LNs are predominately present in subcortical nuclei, e.g. substantia nigra, locus caeruleus, and dorsal motor nucleus of the vagal nerve. In particular, the substantia nigra pars compacta shows severe depletion of pigmented/melanized (45–66%) and dopaminergic (60–88%) neurons, particularly in an area projecting to the striatum (ventrolateral tier). Importantly, PD may present as a multiorgan disease, with α -synuclein pathology involving the central, autonomic, and peripheral nervous systems, but also extraneuronal organs, e.g. the adrenal glands (Jellinger, 2014).

Dementia with Lewy bodies and Parkinson's disease dementia

The distinction between DLB and PDD is primarily based on clinical data; in PDD, the onset of extrapyramidal symptoms should precede dementia by 1 year. Neuropathologically, a significantly more severe A β plaque load in the striatum of DLB than in PDD patients has been observed (Halliday et al., 2011; Jellinger and Attems, 2006). However, on neuropathological post-mortem examination, clinical PDD usually shows the same neuropathological hallmark features as DLB, but A β and tau loads are less severe than in DLB (Jellinger, 2018a). Cognitive deficits in PD patients without dementia are related to age and A β status but are not associated with measurable AD (Winer et al., 2017).

DLB is the second most common age-associated neurodegenerative dementia, accounting for up to 26% of dementias in specialized referral centres (Ince, 2011). The clinical symptoms of DLB are dementia associated with core neuropsychiatric features of fluctuating cognitive function, visual hallucinations, and, in up to 75% cases, mild parkinsonism (McKeith et al., 2017). For a more detailed description of clinical findings in DLB, see Chapter 32.

Macroscopically, brains of DLB patients may appear normal or show diffuse cerebral atrophy that is indistinguishable from AD. The pigmentation of the substantia nigra varies from normal to pale, and the locus caeruleus is usually depigmented. Histologically, DLB is characterized by abundant LBs and LNs in the neocortex, in particular the cingulate gyrus and the limbic system, including the entorhinal cortex and hippocampus. Similar to AD, additional pathologies are usually present in DLB (Z. Walker et al., 2015) and these are discussed in Cerebral multimorbidity, p. 82.

Neuropathological diagnostic criteria for Lewy body disease

Several neuropathological staging systems for LBD are in use:

1. Braak stages for α -synuclein-related pathology postulate that nuclei in the medulla oblongata (e.g. dorsal motor nucleus of the vagus nerve) become initially affected (stage 1) and pathology spreads gradually to the pons (locus caeruleus, stage 2), midbrain (substantia nigra, stage 3), and entorhinal cortex and hippocampus (stage 4), and finally reaches the neocortex (stages 5 and 6) (Braak et al., 2003). Using this classification, PD would reach stage 3, while DLB should at least show stage 4.
2. The Newcastle-McKeith criteria for LBD (McKeith et al., 2005) distinguish between brainstem-predominant (PD), limbic (transitional; DLB), and diffuse neocortical (DLB) types. These criteria differ from Braak stages insofar as they do not strictly postulate a stepwise progression of α -synuclein pathology from the medulla oblongata to the pons, midbrain, limbic areas, and neocortex, and cases might show severe neocortical α -synuclein pathology, with only minimal involvement of brainstem regions.

Therefore, this staging system questions the validity of the system proposed by Braak and colleagues (Braak et al., 2003).

3. Leverenz and colleagues (Leverenz et al., 2008) modified the Newcastle–McKeith criteria by adding an amygdala-predominant type that may completely lack α -synuclein pathology in regions other than the amygdala. This amygdala-predominant type frequently co-occurs with severe AD (e.g. in 24% of otherwise pure AD cases) (Uchikado et al., 2006).

Multiple system atrophy

Multiple system atrophy (MSA) is a sporadic, adult-onset, and fatal neurodegenerative disease, characterized clinically by parkinsonism, cerebellar ataxia, autonomic dysfunction, and corticospinal signs. MSA primarily involves striatonigral and olivopontocerebellar structures (Jellinger and Wenning, 2016). On macroscopic examination, considerable atrophy of the cerebellum and pontine base is frequently observed and the atrophic putamen shows dark discoloration. The substantia nigra and locus caeruleus are depigmented. The characteristic neuropathological lesions of MSA are oligodendroglial α -synuclein cytoplasmic inclusions known as glial cytoplasmic inclusions (GCIs or Papp-Lantos inclusions) that are associated with myelin depletion. α -synuclein also accumulates in oligodendroglial nuclei, as well as in the cytoplasm and nuclei of neurons (Valera and Masliah, 2017) (Fig. 5.7). MSA is currently classified as an oligodendroglioneuronal synucleinopathy with multisystem neurodegeneration (Jellinger, 2018b)

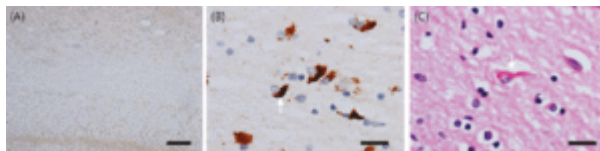


Fig. 5.7

In multiple system atrophy (MSA), aggregates of α -synuclein termed Papp-Lantos inclusions or glial cytoplasmic inclusions (arrows in B and C) are frequent in the oligodendroglia. Photomicrographs are taken from sections of the external capsule. A and B, α -synuclein immunohistochemistry; C, H/E.

Scale bars: A, 500 μ m; B and C, 20 μ m.

Frontotemporal lobar degenerations (including tauopathies)

Frontotemporal lobar degenerations (FTLDs), the third or fourth most frequent cause of dementia, are a heterogeneous group of neurodegenerative diseases that usually show a frontotemporal-pronounced cerebral atrophy (Lashley et al., 2015). Microscopically, they

are characterized by cellular inclusion bodies that are composed of either tau or TDP-43 or a protein encoded by the fused in sarcoma gene (FUS) and/or ubiquitin or neurofilament or a basophilic substance (basophilic inclusion bodies). According to the predominant protein aggregates, the subtypes described in the following sections can be distinguished, but there are cases with overlapping pathology (Mann and Snowden, 2017). A recent review demonstrated their genetic pleiotropy, indicating that sporadic FTLT is a polygenetic disorder (Ferrari et al., 2017). It should be mentioned that FTLT-tau are frequently listed in the group of tauopathies that additionally include diseases that are not characterized by atrophy of frontal and/or temporal lesions such as parkinsonism–dementia complex of Guam and post-encephalic parkinsonism.

FTLT-tau

Pick's disease

Pick's disease (PiD), although a well-known eponym, is a rare cause of frontotemporal dementia (<5% of FTLT cases), with behavioural abnormalities or with non-fluent progressive aphasia as the most common clinical presentation. Both sexes are equally affected, with an average age of onset at approximately 60 years and a disease duration of 8–10 years (Munoz et al., 2011). At post-mortem examination, the characteristic macroscopic feature is severe, circumscribed atrophy of the frontal, temporal, and sometimes parietal lobes, while the motor and sensory cortices, posterior two-thirds of the superior temporal gyrus, and occipital cortex are preserved. The brainstem and cerebellum show no macroscopic abnormalities. Histologically, the macroscopically atrophic areas, as well as the deep grey matter and the brainstem, in particular the monoaminergic nuclei, show neuronal loss and gliosis, which also affects the atrophic subcortical white matter. Pick bodies—the neuropathological hallmark lesion of PiD—are large argyrophilic, neuronal, cytoplasmic, round inclusions, predominately composed of 3R tau. Pick bodies are frequent in hippocampal pyramidal neurons of the CA1 sector, while CA2–4 and subiculum are less frequently involved. In other cortical areas, Pick bodies may occur less evenly distributed, but in large clusters (Irwin et al., 2016). Ballooned neurons, similar to the ones seen in corticobasal degeneration (CBD), may be present, as well as tau-immunoreactive glial lesions that, interestingly, are predominately composed of 4R tau (Zhukareva et al., 2002).

Corticobasal degeneration

The clinical symptoms in CBD are highly variable, the most characteristic being the corticobasal syndrome with asymmetrical akinetic-rigid parkinsonism and cortical signs, including apraxia, dystonia, and myoclonus. However, some autopsy series indicate that—although being characteristic—the corticobasal syndrome may not be the most common clinical presentation of CBD, as frontal-type dementia has been reported to be more frequent. No epidemiological data are available for the

prevalence and incidence of CBD, but its incidence has been estimated to be <1 per 100,000 people per year. CBD is a disease of middle to late age, with no gender predisposition and age being the only known risk factor (Dickson et al., 2011). Reflecting the broad spectrum of possible clinical presentations, the neuropathological findings in CBD are highly variable (Lee et al., 2011). However, the classical presentation shows asymmetrical atrophy of cortical gyri that is most marked in superior frontal and parietal parasagittal regions. Among other macroscopic features, a red-brown discoloration may be seen in the globus pallidus and the substantia nigra shows loss of neuromelanin pigment, while the locus caeruleus appears normal. The characteristic neuropathological finding of CBD is the accumulation of 4R tau in the neuropil and astrocytes in the cortex, white matter, basal ganglia, thalamus, and brainstem. 4R tau may also be present in neurons, but the neuropathological hallmark lesion is the astrocytic plaque, which is not seen in other diseases. The early prominence of the astrocytic plaques suggests that CBD begins as an astrogliaopathy, while neuronal lesions represent the predominant lesion type in advanced disease (Ling et al., 2016). The astrocytic plaque represents 4R tau accumulation in distal segments of astrocytes, while the cell body is free of accumulation. This morphology is reminiscent of an NP, but no A β accumulation is present in astrocytic plaques. Astrocytic plaques predominately occur in the cortex but can also be present in other regions such as the caudate and putamen. Swollen cortical neurons that are termed ballooned neurons are another neuropathological hallmark of CBD.

Progressive supranuclear palsy

Symmetrical, akinetic-rigid parkinsonism with severe postural instability and supranuclear ophthalmoplegia are the typical clinical symptoms of progressive supranuclear palsy (PSP) (Steele–Richardson–Olszewski syndrome) (Höglinger et al., 2017), but less frequent atypical presentations, such as asymmetrical clinical syndromes (e.g. corticobasal syndrome), may be seen (Ling et al., 2016). In the UK, the prevalence of PSP is estimated at approximately 5 per 100,000, with the mean age at onset ranging from 66 to 69 years (Nath et al., 2001), while it is 10 per 100,000 in Japan (Yoshida et al., 2017). The basal ganglia, subthalamic nucleus, and substantia nigra are primarily affected, and usually pathology in the cerebellar dentate nucleus is severe and associated with profound atrophy of the superior cerebellar peduncle. The characteristic neuronal lesion is the globose NFT that is composed of 4R and occurs in the brainstem nuclei and the nucleus basalis of Meynert, while in other regions, NFTs may be flame-shaped. Immunohistochemistry for 4R tau also labels tuft-shaped astrocytes (tufted astrocytes), which are the most characteristic glial lesion in PSP (Yokoyama et al., 2016). In addition, 4R-positive NTs are seen in the grey and white matter of both cortical and subcortical regions. The severity and distribution of tau pathology vary in the different subtypes of PSP (PSP-parkinsonism/PSP-P, Richardson's

syndrome, and atypical forms), causing a broad spectrum of clinical phenotypes (Respondek et al., 2017).

Argyrophilic grain disease

Argyrophilic grain disease (AGD) has a mean age of onset of approximately 80 years, with males and females affected equally. AGD is the most common sporadic tauopathy and is observed in up to 5% of late-onset dementia cases (Saito et al., 2002). However, AGD is a frequent finding in other neurodegenerative diseases and has been reported to be present in varying severity in up to 26% of AD cases (Fujino et al., 2005). Macroscopically, the brain appears relatively normal, with mild frontotemporal cortical atrophy, but severe atrophy of the ambient gyrus was described in late stages of the disease (Saito et al., 2002). In AGD, 4R tau aggregates occur in dendrites and present as comma- or grain-shaped structures in the neuropil of the medial temporal lobe, in particular in the hippocampal Ammon's horn sector CA1 and prosubiculum. In addition, 4R tau is present in oligodendroglia, referred to as coiled bodies, that may be present in other tauopathies, but in AGD, they are a consistent finding in the white matter. AGD differs from other tauopathies by lacking tau acetylation (Grinberg et al., 2013).

FTLD with TDP-43 pathology

FTLD with TDP-43 pathology (FTLD-TDP) may underlie any of the three major clinical variants of the frontotemporal dementia syndrome, behavioural variant, progressive non-fluent aphasia, and semantic dementia (Alafuzoff et al., 2015). It has been shown that neuropathologically, FTLD-TDP is present in 50% of cases with clinical frontotemporal dementia syndrome (Neumann et al., 2006), with 20–40% being associated with a positive family history with various disease-causing mutations. The mean age of onset of FTLD-TDP is approximately 60 years (33–89 years), with a mean disease duration of 8 years (2–18 years). FTLD-TDP can be categorized into four distinct histopathological patterns of TDP-43 pathology (types A to D), with an additional rapidly progressive subtype 'E' (Lee et al., 2017). Neuropathologically, FTLD-TDPs are characterized by neuronal cytoplasmic inclusions (NCIs) that consist of phosphorylated TDP-43. TDP-43 is involved in regulating transcription and alternative splicing (Alafuzoff et al., 2015); physiologically, TDP-43 is present in the nucleus, but under pathological conditions, such as FTLD-TDP, it is usually located in the cytoplasm (TDP-43 NCIs in spinal motor neurons are a characteristic feature of ALS). Macroscopically, cerebral atrophy is variable, but frontal and temporal lobes are most frequently affected, sometimes with asymmetrical distribution. In addition to unspecific features of neurodegeneration, TDP-43-positive NCIs and dystrophic neurites (DNs) are usually seen in the frontotemporal neocortex and granule cell layer of the dentate gyrus (Mackenzie et al., 2010) (Fig. 5.8). Neuronal intranuclear inclusions (NIIs) may also be present and, depending on the amount and distribution of NCIs and DNs, as well as on the presence of

NIIs, four neuropathological subtypes (types A, B, C, and D) of FTLD-TDP have been described (Lee et al., 2017; Mackenzie et al., 2011; Yousef et al., 2017).

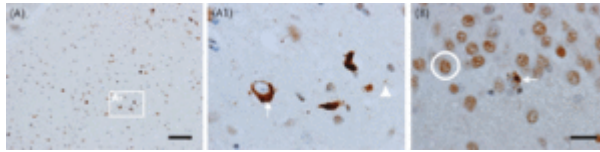


Fig. 5.8

TDP-43 positive neuronal cytoplasmic inclusions (NCI, arrow in A1 and B) and thread-like structures (arrowhead in A1) are the characteristic neuropathological lesion for FTLD-TDP-43 and motor neuron disease (amyotrophic lateral sclerosis) but may be present as an unspecific feature in a variety of other diseases, including AD. Of note, under physiological conditions TDP-43 is present in neuronal nuclei (ring in B). Immunohistochemistry with antibody against (nonphosphorylated) TDP-43.

Scale bars: A, 100 μ m; B, 20 μ m.

FTLD-UPS

Ubiquitin-positive inclusions are the characteristic lesion of FTLD-UPS (ubiquitin-proteasome system). It now appears that most cases of sporadic FTLD-UPS have FUS-immunoreactive pathology, but the term FTLD-UPS is still appropriate for a familial form of FTLD—familial FTLD linked to chromosome 3 (FTD-3). Brains show frontotemporal atrophy, cortical microvacuolation, neuronal loss, and astrogliosis. The remaining neurons show enlarged vacuoles (Lashley et al., 2015).

FTLD-FUS

FTLD-FUS are characterized by abnormal accumulation of a nuclear DNA/RNA-binding protein, encoded by the fused in sarcoma (*FUS*) gene, as the most prominent pathology and include atypical FTLD with ubiquitinated inclusions (aFTLD-U), neuronal intermediate filament inclusion disease (NIFID), and basophilic inclusion body disease (BIBD) (Mackenzie et al., 2010). A more detailed description of FTLD-FUS is beyond the scope of this chapter. For a review, see Mackenzie and Neumann, 2017.

FTLD with no inclusions

The term FTLD-no inclusions (FTLD-ni) is used for FTLD cases that lack any histochemically and immunohistochemically detectable inclusions but otherwise show clinical features of dementia and non-specific neuropathological changes (e.g. atrophy, neuronal loss). This type has previously been referred to as 'dementia lacking distinctive

histopathology' (DLDH), but it is suggested that FTL D-ni replaces the term DLDH, as the latter suggests that pathological lesions are completely absent (Mackenzie et al., 2009).

Perry syndrome

Perry syndrome (PS) is a rare atypical parkinsonism, with depression, apathy, weight loss, and central hypoventilation, caused by mutations in the dynactin p150^{glued} (*DCTN1*) gene, with TDP-43 inclusions as the defining morphological feature. PS has NCIs, DNIs, and frequent perivascular astrocytic inclusions (PVIs) and spheroids, which are different from other TDP-43 proteinopathies (ALS, FTL D with or without motor neuron disease) and HS (Mishima et al., 2017). Pallidonigral TDP-43 proteinopathy is the underlying pathological process (Dickson, 2018).

Huntington's disease

Huntington's disease (HD) is an autosomal dominant hereditary disease. HD belongs to the family of trinucleotide repeat diseases that are caused by expansions of pre-existing tandem repeat sequences, with each of the diseases (e.g. myotonic dystrophy type 2, spinocerebellar ataxia) affecting different genes. There is recent evidence suggesting that HD is a new member of the family of tauopathies, but this awaits further confirmation (Gratuzi et al., 2016). The gene for HD (*huntingtin* or HTT) is located on the short arm of chromosome 4 (4p16.3), and the mutation consists of an expanded repetition of the cytosine-adenine-guanine (CAG) trinucleotide. HD equally affects men and women; age at diagnosis is, on average, 40 years, and the symptomatic prevalence ranges from 5 to 10 per 100,000, with global variations in its prevalence (Baig et al., 2016; Rawlins et al., 2016). The prodromal period of HD commonly includes neuropsychiatric symptoms, such as depression and psychosis, as well as motor features (subtle involuntary movements and oculomotor dysfunction), and these may be present for many years before the diagnosis in attenuated form. Typical symptoms of the disease include chorea and mental dysfunction, leading to dementia. The neuropathology of HD shows a multisystem degeneration which, apart from the striatum, affects the neo- and allocortex, thalamus, pallidum, brainstem, and cerebellum, sharing similarities with polyglutamine spinocerebellar ataxias (Rüb et al., 2016). The brain in end-stage HD shows severe reduction in weight (900–1000 g), mainly due to profound atrophy of the caudate nucleus and putamen, but the cerebral cortex, hippocampus, thalamus, and white matter are also affected. Microscopically, the basal ganglia show severe neuronal loss and gliosis, and on microscopic examination, huntingtin or ubiquitin-positive protein accumulations are frequently seen in cellular processes (neurites) and, to a lesser degree, as nuclear inclusion bodies. A rating scale of five grades (0–4) designating the order of severity of neuropathological involvement correlates closely with the extent of clinical disability (Rüb et al., 2016; Singh-Bains et al., 2016; Vonsattel et al., 1985). HD-like (HDL) 2 is an autosomal dominant disorder with adult

onset that shows very similar neuropathological features, suggesting overlapping pathogenesis (Govert and Schneider, 2013, Rudnicki et al., 2008).

Prion diseases

Prion diseases that are also known as transmissible spongiform encephalopathies (TSEs) are caused by a potentially infectious agent and thereby differ from other neurodegenerative diseases. The infectious agent is the prion protein (PrP) that essentially consists of PrP^{Sc} which presents as aggregates of an abnormally folded β -sheet-rich isoform of a normal cellular protein of largely unknown function (possible role in myelin maintenance), termed PrP^C (Aguzzi and Heikenwalder, 2006). Prion diseases occur in humans and animals. Human prion diseases encompass sporadic [sporadic Creutzfeldt-Jakob disease (sCJD) and fatal sporadic insomnia], inherited (familial CJD, Gerstmann-Sträussler-Scheinker syndrome, and fatal familial insomnia), and infectious forms (iatrogenic CJD, variant CJD (vCJD), and Kuru). Of note, as vCJD predominately occurred in the UK, the country with the highest incidence of bovine spongiform encephalopathy (BSE), a bovine prion disease, exposure to prion proteins due to past consumption has been suggested to cause vCJD in humans. It is assumed that PrP^{Sc} is capable of inducing conformational conversion of PrP^C into PrP^{Sc}, thereby leading to a spread of aggregated PrP^{Sc} in the CNS.

The most common form of prion disease in humans is sCJD, accounting for 85% of all CJD cases. No cause for sCJD has been identified, and the typical clinical picture is rapidly progressive dementia with ataxia and myoclonus. The incidence of sCJD is between 1 and 2 cases per million per year, and the mean age of onset is 65 years. On macroscopic examination, the brain may appear normal, but usually some degree of atrophy is present. Histologically, sCJD is characterized by a triad of spongiform change, neuronal loss, and astrocytic, as well as microglial, gliosis. Spongiform change presents as diffuse or focal small, round or oval vacuoles in the cerebral cortex (whole thickness or deep layers), subcortical grey matter (almost constantly in the head of the caudate nucleus), and cerebellar molecular layer. In addition, PrP immunohistochemistry should be used to confirm the diagnosis. A consensus classification of human prion disease subtypes allows reliable identification of molecular subtypes (Barron et al., 2016). While most cases of prion disease are idiopathic and acquire the disease through an identified source of infection, about 10–15% of patients are affected by a genetic form and carry either a point mutation or an insertion of octapeptide repeats in the *PrP* gene—such as Gerstmann-Straussler-Scheinker syndrome or fatal familial insomnia (Honda et al., 2017).

Vascular dementia

VaD, or vascular cognitive impairment, can be defined as acquired cognitive impairment caused by cerebrovascular disease. Due to the high variability of morphological findings and multifactorial pathogenesis of VaD, no generally accepted morphologic scheme for staging cerebrovascular lesions and no validated neuropathological criteria for VaD have been established (Jellinger, 2013). Therefore, many aspects of VaD, such as prevalence, morphology, and pathogenesis, are a matter of ongoing discussions. The recently established 'Vascular Cognitive Impairment Neuropathology Guidelines' (VCING) are based on the assessment of occipital CAA, arteriolosclerosis in the occipital white matter, and infarcts. This assessment allows to state the likelihood (low, <50%; moderate, 50–80%; high, >80%) that cerebrovascular disease contributed to cognitive impairment (Skrobot et al., 2016). VaD has, however, been suggested to be the cause for dementia in approximately 10% of cases. Clearly, cerebrovascular lesions can cause neuronal loss and—depending on the topographical localization—this process may lead to dementia (Iadecola, 2013; Jellinger, 2016; Thal et al., 2012).

The morphological substrates for VaD are extensive, and only a brief and incomplete description can be provided here (for comprehensive reviews, see Grinberg and Thal, 2010 and McAleese et al., 2016).

Two types of vessel disorders can potentially cause VaD:

1. Atherosclerosis is a very common vessel disorder in the older person, frequently affecting large to medium-sized arteries of the entire cardiovascular system. In the cranium, it often affects the circle of Willis, and an important extracranial site—with respect to the development of cerebrovascular lesions—is the carotid arteries, in particular at the level of the carotid bifurcation. Atherosclerosis is initiated by thickening of the tunica intima (i.e. the innermost layer of a blood vessel), with subsequent accumulation of blood-derived lipids. This process is followed by splitting of the internal elastic lamina, and finally cholesterol accumulation leads to the manifestation of atherosclerotic plaques that can calcify. Atherosclerosis causes narrowing of the arteries' lumina, thereby reducing the blood supply for the supported region, but this is frequently compensated by a shift in blood flow towards collateral arteries (e.g. vertebral arteries for the internal carotid arteries). On the other hand, rupture of atherosclerotic plaques often leads to thrombosis that results in either occlusion of the lumen or thromboembolism. Depending on the size of the embolus, thromboembolism may cause lesions that range from 'silent infarcts' to large cerebral infarcts with overt clinical symptoms.
2. Small vessel disease refers to pathological changes that affect small arteries and arterioles (Fig. 5.9). Small arteries may show morphological changes that are similar to atherosclerotic changes (i.e. microatheroma) and are termed 'small vessel arteriosclerosis/

atherosclerosis'. 'Lipohyalinosis' is used for asymmetric fibrosis/hyalinosis, while concentric hyaline thickening with lumen stenosis is termed 'arteriosclerosis'. The latter is particularly common in the white matter and the main cause for white and deep grey matter lesions, respectively.

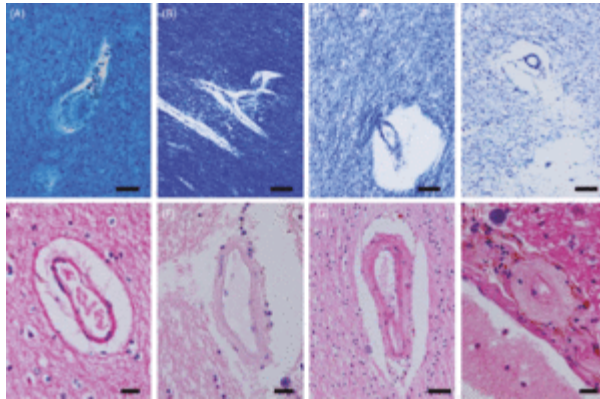


Fig. 5.9

Small vessel disease is a frequent cause of white matter (WM) lesions. (A) Normal vessel and white matter; note the slight perivascular space that is regarded as an artifact; (B) mildly enlarged perivascular spaces; (C) considerable enlargement of the perivascular space accompanied by moderate demyelination of the WM (pallor in myelin staining); (D) severe WM lesions with enlarged perivascular spaces, WM pallor, and tissue loss; (E) normal artery; (F) artery with mild fibrosis; (G) artery with moderate fibrosis; (H) severe arteriolar fibrosis with acellular concentric thickening of the vessel wall (usually associated with hypertension). A-D, Luxol Fast Blue histochemistry (myelin stain); E-H, H/E.

Scale bars: A and G, 50 μ m; B, C, D, and H, 100 μ m; E and F, 20 μ m.

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White matter lesions (leukoaraiosis) are increasingly detected by modern neuroimaging methods (on MRI, such lesions are present in most older people), frequently clinically asymptomatic, and in most cases related to small vessel disease of the white matter. The associated neuropathological findings include demyelination, axonal loss, and lacunar infarcts (usually small), most frequently in the frontal, parietal, and occipital white matter. Using special stains (e.g. Luxol fast blue), demyelination is indicated by a pallor in staining intensity, and arterioles in these areas may show concentric thickening of the vessel wall and perivascular spaces that are filled with macrophages (of note, small perivascular spaces alone are not an indicator of small vessel disease but are an artefact caused by tissue processing; Fig. 5.9). Lacunes are cavities measuring 5–10 mm in diameter that are caused by either old (lacunar) infarcts or, less frequently, haemorrhages. In addition to the

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white matter, they occur in the basal ganglia (deep grey matter lesions) and, if severe, are the morphologic substrate of the so-called status lacunaris or *état criblé*.

Ischaemic brain infarcts are caused by insufficient blood supply frequently due to thromboembolism. After 6–12 hours, the neurons show signs of acute ischaemic cell injury (e.g. eosinophilic cytoplasm and shrunken nucleus), and between 24 and 48 hours, neutrophils appear that are replaced by macrophages after 48 hours. Ten days after the infarction, the area is liquefied, resulting in the formation of a cavity (third week) that becomes intersected by vascular and connective tissue strands and surrounded by gliosis (scarring; Fig. 5.10). Haemorrhagic brain infarcts are characterized by secondary blood influx into the infarcted territory, and microinfarcts refer to infarcts below 5 mm in diameter (for lacunar infarcts, see earlier).

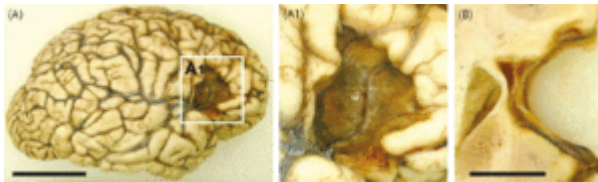


Fig. 5.10

Old cystic infarct in the right frontal lobe in the territory of the middle cerebral artery (A; B, frontal plane).

Scale bars: A, 50 mm; B, 20 mm.

Cerebral haemorrhages are larger than 10 mm in diameter. Causes for non-traumatic intracerebral haemorrhage include aneurysms of cerebral arteries, coagulation disorders, atherosclerosis, hypertension with small vessel disease, and CAA. Recently, cerebral microbleeds (i.e. haemorrhage not visible to the naked eye) have gained wider attention, as MRI detects small signal voids, indicating perivascular accumulation of haemosiderin/haemosiderin-laden macrophages that are presumed to reflect old cerebral microbleeds. Cerebral microbleeds are associated with CAA and, according to MRI studies, are frequent in older people (e.g. 23.5%) (Vernooij et al., 2008). However, microbleeds are rarely seen at neuropathological post-mortem examination and their true incidence is therefore controversial.

It is beyond the scope of this chapter to provide a comprehensive review of the many possible ways to classify cerebrovascular pathology, and several articles are suggested for further reading (Gorelick et al., 2011; Kalaria, 2016; McAleese et al., 2016). As an example, a brief outline of the classification of VaD, according to the underlying disease, is provided here.

1. Large vessel disease: atherosclerosis of extra- or intracranial arteries may cause thromboembolism or hypoperfusion that leads to single or multiple infarctions in the cerebral regions that receive blood supply by the respective artery. Cognitive impairment might result from smaller infarcts that are strategically placed, affecting functionally important brain areas and neuronal circuits ('strategic' infarct dementia syndrome).
2. Small vessel disease: small vessel disease affects small arteries and arterioles and includes arteriosclerosis/atherosclerosis, arteriolosclerosis, and lipohyalinosis. Small vessel disease may cause ischaemic white matter damage and lacunar infarcts in the basal ganglia, both of which may present a morphological correlate for VaD.
3. Hypoxic damage: this is caused by cerebral hypoperfusion and may lead to ischaemic-anoxic damage and HS (see Hippocampal sclerosis, p. 84).

Cerebral multimorbidity

It is becoming increasingly clear that the ageing brain is characterized by the presence of multiple pathologies, rather than the characteristic neuropathological lesions of one single neurodegenerative disease only. Of particular importance is the frequent presence of other pathologies in the aged brain that coexist with AD, e.g. cerebrovascular disease, LB pathology, AGD, TDP-43 pathology, and HS (Jellinger and Attems, 2015).

As already outlined, neurodegenerative diseases are neuropathologically characterized by the presence of discrete lesions in a specific topographical pattern. However, data from many different autopsy studies point towards the presence of additional lesions in otherwise well-characterized cases, which fulfil the criteria for a single distinct disorder (Jellinger and Attems, 2007b; Jellinger and Attems, 2010; Kovacs et al., 2008; Rahimi and Kovacs, 2014) (Fig. 5.11):

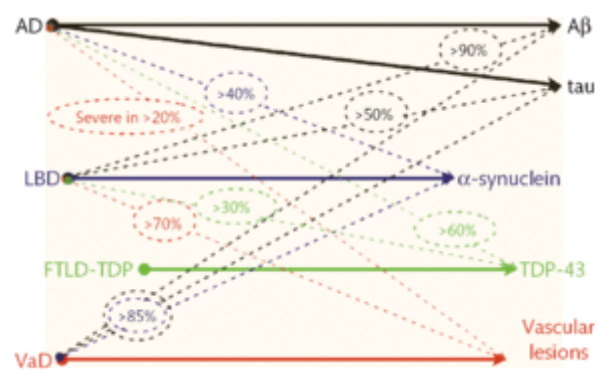


Fig. 5.11

Multiple pathologies in brains of older demented patients. Full arrows point towards the characteristic neuropathology of the respective disease, while dotted arrows point towards neuropathological lesions that are frequently seen in addition to the main pathological hallmark lesions. Approximate percentages are encircled.

AD, Alzheimer's disease; LBD, Lewy body diseases; FTLD-TDP, frontotemporal lobar degeneration with TDP-43 pathology; VaD, vascular dementia.

In AD that is characterized by A β and tau pathology, LBs are seen in up to 43% (Uchikado et al., 2006) (AD with amygdala LBs is considered a distinct form of α -synucleinopathy) and severe cerebrovascular lesions in up to 20% of cases, respectively (Jellinger and Attems, 2007b). TDP-43 pathology following a distinct hierarchical spreading pattern (which is different from FTLD-TDP) is seen in up to 70% of AD cases and, if severe, has a strong independent effect on cognition, memory loss, and medial temporal lobe atrophy (Josephs et al., 2014; McAleese et al., 2017a). Of note, such TDP-43 pathology is also present in LBD (33%) and cognitively unimpaired elderly controls (18%), suggesting that the prevalence of this type of TDP-43 pathology increases with advancing age (McAleese et al., 2017a).

In LBD that is characterized by α -synuclein pathology, A β pathology was identified in 95%, considerable tau pathology (Braak stages V/VI) in 55%, and various degrees of cerebrovascular pathology in 75% of cases (Jellinger and Attems, 2008). In another large clinicopathological cohort of over 200 DLB/PDD cases, 26% had additional low, 21% intermediate, and 30% high AD neuropathologic changes, respectively (Irwin et al., 2017). The latter group, showing neocortical LBD, together with high AD neuropathologic changes, can be classified as mixed dementia, since the amount of each LB and AD pathology would be sufficient to cause clinical dementia (L. Walker et al., 2015).

Pure VaD without additional lesions is rare, and frequently additional, often limited, AD pathology is present. However, since 50–85% of post-mortem brains from individuals (with and without dementia) who die over 80 years of age show appreciable cerebrovascular lesions, a particular problem is the impact of cerebrovascular disease on cognition, especially in relation to AD pathology (Kapasi et al., 2017).

The high prevalence of multiple pathologies in the brains of aged individuals could reflect the simultaneous presence of one single distinct neurodegenerative disease and age-related changes that are not directly associated with the primary neurodegenerative disease; for example, the high prevalence of cerebrovascular lesions in AD brains of individuals aged 80+ years probably mirrors the prevalence of age-associated vascular diseases in the aged per se, rather than suggesting causal relationships between AD and cerebrovascular lesions. The burdens of vascular and AD-type lesions are indeed considered to be independent of each other and are consistent with an additive (or even synergistic) effect of both types of lesions on cognitive impairment. The thresholds for vascular and degenerative lesions in distinguishing 'pure' VaD or AD from mixed cases have been critically discussed (Gold et al., 2007). AD pathology alone more frequently accounts for dementia than both microscopic and macroscopic infarcts, and in advanced stages of AD, concomitant small vascular lesions do not significantly influence the overall state and progression of cognitive decline; hence, the severity and extent of AD pathology seem to overwhelm the effects of cerebrovascular disease (Jellinger, 2007a). However, this does not preclude the possibility that cerebrovascular lesions exert an influence on AD pathology itself and it has been suggested that cerebrovascular lesions in AD lower the threshold for overt clinical dementia, i.e. less AD pathology is needed to cause clinical symptoms, if additional cerebrovascular pathology is present (Kapasi et al., 2017).

Another example of the simultaneous presence of a distinct neurodegenerative disease and age-associated change would be limited AD pathology (e.g. Braak stage III and A β -plaques) in DLB; here, AD pathology could be regarded as age-associated change that manifests independently of DLB. Similarly to the presumed impact of cerebrovascular lesions in AD, α -synuclein pathology in DLB might be aggravated by age-associated AD pathology.

Co-occurrence of abnormal depositions of tau, α -synuclein, and/or A β suggests an interaction between these misfolded proteins in the human brain, and such an interaction is supported by studies in animal models. *In vitro* studies demonstrated synergistic fibrillization of tau and α -synuclein (Giasson et al., 2003), and data from studies on transgenic (tg) mice indeed suggest a mutual interaction of A β , tau, and α -synuclein pathologies; Clinton and colleagues crossed 3 $\times$ tg mice that develop both A β plaques and tau pathology with mice that express the A53T mutation in α -synuclein (M83-h) (Clinton et al., 2010). At 12 months of age, these so-called DLB-AD mice had significantly higher detergent-soluble and

insoluble A β ₄₀, detergent-insoluble A β ₄₂, and insoluble tau levels than 3 $\times$ tg mice, respectively. Moreover, detergent-insoluble α -synuclein as well as detergent soluble α -synuclein phosphorylated at serine 129 levels were significantly higher in DLB-AD mice, compared to M83-h mice. Taken together, these results suggest that A β , tau, and α -synuclein interact *in vivo* to promote the aggregation and accumulation of each other.

Recent studies suggest similar interactions in human brains; for example, in DLB cases, cerebral α -synuclein scores increased with increasing AD pathology (Irwin et al., 2017) and in PDD and PD cases, a significant correlation between LB scores and NFT Braak stages was found (Compta et al., 2011). These findings suggest: (1) a synergistic or triggering effect between tau, α -synuclein, and A β pathologies (Spires-Jones et al., 2017), as increasing levels of AD pathology may induce a higher burden of α -synuclein pathology, and vice versa (Guo et al., 2013); (2) an overlap in the pathology between various proteinopathies; and (3) the cognitive decline and related symptoms in LBDs may not always be solely a consequence of α -synuclein-induced neurodegeneration, but also due to additional AD-related pathologies, and hence mixed pathologies may contribute to the clinical symptoms (Colom-Cadena et al., 2017; Howlett et al., 2015; Irwin et al., 2017; Kapasi et al., 2017; Spires-Jones et al., 2017; Z. Walker et al., 2015). On the other hand, the considerable overlap between tau and α -synuclein pathologies could be explained by a mechanistic linkage between tauopathies and synucleinopathies (Jellinger, 2018a).

In summary, keeping in mind that prevalence rates of A β , tau, α -synuclein, TDP-43, and cerebrovascular pathologies all increase with advancing age (Spires-Jones et al., 2017), it is no surprise that, for example, a considerable proportion of AD patients will show additional α -synuclein and/or TDP-43 and/or cerebrovascular pathologies; otherwise AD, as such, would be protective against other age-associated cerebral pathologies, which, quite clearly, is not the case. On the contrary, it rather seems that different pathologies aggravate each other, and hence future patient stratification should be based on the actual pathologies present in the brain, rather than on distinct diseases (e.g. AD, DLB, etc.). The latter approach introduces a considerable bias into all types of clinical studies, as it assumes that clinical cohorts are homogenous with regard to their underlying pathology, while they are actually highly heterogenous due to the high prevalence of cerebral multimorbidity in old age.

Future directions in neuropathological assessment

Currently, neuropathological assessment is based on semi-quantitative scoring, usually on a four-tiered scale, e.g. 0, absent; 1, mild; 2, moderate; 3, severe. Frequently, the criteria for scoring one of those categories have been standardized. While semi-quantitative assessment allows for the statement of routine diagnoses, it provides only a rough estimation of the amount of pathology present. For example, Walker and

colleagues found that the area covered by immunopositivity for the AT8 antibody (tau) in cases that were assigned the score 'severe' may differ by nearly 50% between cases (Walker et al., 2017). In the 90+ study, a prospective, longitudinal, population-based study of ageing and dementia, the area covered by A β immunopositivity in selected neocortical regions significantly correlated with the presence of clinical dementia (Robinson et al., 2011); of note, in most studies, the extent of neocortical A β immunopositivity, as assessed by semi-quantitative scoring, did not correlate with the presence of clinical dementia. It is likely that new clinicopathological phenotypes could be identified by routinely assessing the amount of pathology in a more quantitative way. Indeed, in quantitatively assessing tau pathology in a large cohort ($n = 889$) of neuropathologically diagnosed AD cases, hippocampal sparing and limbic-predominant subtypes of AD were found, which differed from typical AD in clinical presentation, age at onset, disease duration, and rate of cognitive decline (Murray et al., 2011). Given that quantitative assessment of tau pathology alone in AD cases points towards new clinicopathological phenotypes, we believe that a more accurate, quantitative assessment of various neuropathological lesions is necessary to further elucidate possible mutual relationships between pathologies, as well as their combined influence on the clinical picture (Walker et al., 2017). A deeper knowledge of underlying pathologies in age-associated neurodegeneration and cerebrovascular disorders is paramount to identify suitable targets for new therapeutic approaches.

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Biomarkers for Alzheimer's disease

Chapter: Biomarkers for Alzheimer's disease

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Introduction

Recent years have witnessed an increasing understanding of the molecular and cellular underpinnings of Alzheimer's disease (AD) (Winblad et al., 2016). The complex pathophysiology of AD involves a series of interconnected pathophysiological pathways, including—extracellular accumulation of the 42-amino acid-long amyloid beta (A β 1–42) peptide into oligomers, fibrils, and plaques as well as the accumulation of intraneuronal neurofibrillary tangles—and downstream processes such as widespread neuroinflammation (Heneka et al., 2015). These events ultimately induce neurodegeneration and synaptic dysfunction with disruption of physiological neural connectivity (Spire-Jones and Hyman, 2014). Hence, several molecular alterations take place in the AD brain, including, but not restricted to, the following: (1) alterations in amyloid precursor protein (APP) and tau protein homeostasis (O'Brien and Wong, 2011); (2) mitochondrial dysfunction; (3)

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increased oxidative stress (Verri et al., 2012); (4) lipid dishomeostasis (Giannopoulos et al., 2014); and (5) membrane and cell trafficking dysregulation (Di Paolo and Kim, 2011). These molecular pathways are linked with each other and with (epi)genetic factors; thus, a systems biology approach to explore different molecular networks is needed to fully untangle the pathogenesis and pathophysiology of AD (Kaddurah-Daouk et al., 2013; Noorbakhsh et al., 2009).

Different research criteria, integrating the use of biomarkers of AD pathophysiology, have been introduced for the diagnosis of AD: the International Working Group (IWG)-1 (Dubois et al., 2010), IWG-2 (Dubois et al., 2014), and the National Institute of Aging and Alzheimer's Association (NIA-AA) criteria (Albert et al., 2011). These criteria facilitate the identification of early stages of AD including the definition of mild cognitive impairment (MCI) and provide guidance on how to interpret biomarker alterations (Visser et al., 2012).

The IWG criteria use the term 'prodromal AD' for the diagnosis of AD and were intended to serve as research criteria. The IWG-1 criteria require episodic memory impairment and at least one abnormal AD biomarker; this can be either (1) a topographical marker (evidence of medial temporal lobe atrophy on structural MRI or parieto-temporal hypoperfusion on ^{18}F -fluorodeoxyglucose-positron emission tomography [^{18}F -FDG-PET]) or (2) a pathophysiological marker (decreased CSF concentrations of A β 1-42, increased CSF concentrations of tau protein, or increased amyloid PET uptake) (Dubois et al., 2007, 2010).

The IWG-2 criteria include cognitive impairment in any cognitive domain and either (1) reduced CSF A β 1-42 concentrations, along with increased CSF tau, or (2) increased amyloid PET uptake (Dubois et al., 2014). Two subcategories are defined by the IWG-2 criteria: typical prodromal AD (if impairment on a memory test is observed) and atypical prodromal AD (if only impairment on a non-memory test is observed).

The NIA-AA criteria use the definition 'MCI due to AD' and were proposed for both clinical and research uses. They require: (1) the presence of cognitive impairment in any cognitive domain and either (2) abnormal amyloid markers (reduced CSF A β 1-42 concentrations or increased amyloid PET uptake) or (3) neuronal injury markers (evidence of medial temporal lobe atrophy on structural MRI, increased CSF tau concentrations, or parieto-temporal hypoperfusion on ^{18}F -FDG-PET).

Substantial disagreements exist between these sets of criteria with reference to staging, nomenclature, and interpretations of biomarker findings. Moreover, in spite of the importance of associating biomarkers with clinical findings, a purely biomarker-based classification scheme is expected to have the widest approval if it is totally independent of any clinically definite diagnostic model, given the lack of consensus on competing definitions (Jack et al., 2016). In this respect, the recently introduced 'A/T/N' scheme is increasingly gaining support. This is a

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dissection model including three binary (positive/negative) categories of biomarkers, based on the nature of the underlying pathophysiology that each biomarker measures: 'A' indicating brain overaccumulation of A β (CSF A β 1-42 or amyloid-PET); 'T' indicating tau hyperphosphorylation (CSF p-tau or tau-PET); and 'N' indicating a quantitative or topographic biomarker of neurodegeneration or neuronal injury (CSF t-tau, ¹⁸F-FDG-PET, or structural MRI). Since each individual score is represented in an 'A $\pm$ /T $\pm$ /N $\pm$ ' arrangement, eight different profiles (combinations) can be generated. This stratification model is agnostic to the hypothesized temporal ordering of AD pathophysiology (i.e. that amyloid precedes tau which, in turn, precedes neural loss). Since it does not require any disease labels, it cannot be considered a diagnostic classification; rather, it is a descriptive approach facilitating the categorization of multi-domain biomarker findings (Jack et al., 2016).

Role of biomarkers in the diagnosis and treatment of Alzheimer's disease

A biomarker is defined as a 'characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or response to an exposure or intervention, including therapeutic interventions. A biomarker is not an assessment of how an individual feels, functions, or survives' (FDA-NIH Biomarker Working Group, 2016). Biomarkers have achieved a crucial role in drug development in all therapeutic areas. Thanks to progress in clarifying pathophysiological mechanisms at a molecular level, as well as in diagnostics and pharmacogenomics, biomarkers have been designated as tools to facilitate all phases of drug discovery and development programmes (Hampel and Lista, 2013). For example, they can be used in clinical trials to support proof of mechanism and increase diagnostic accuracy for AD, thus improving individuals' enrolment (Blennow et al., 2014). Moreover, biomarkers can potentially support patient stratification to achieve better clinical response, can be used to monitor the progression of disease and response to therapy, can identify prognostic molecular signatures, and can underpin diagnostic assays (Blennow et al., 2014). Consequently, biomarkers are integrated in research and development strategies to identify novel candidate drugs, from discovery to regulatory authorization (Hampel et al., 2010a; Vellas et al., 2013). Starting from these premises (Lista et al., 2015a), biomarkers are commonly organized in several categories: (1) target engagement biomarkers, testing hypothesized interaction of a candidate drug with its molecular target; (2) mechanism of action biomarkers, assessing downstream biochemical effects; (3) outcome biomarkers, assessing efficacy and safety; (4) safety biomarkers, more specifically assessing and predicting tolerability and side effects; and (5) theragnostic biomarkers, supporting therapeutic choices through the prediction of both the most appropriate therapy (or response to therapy) for an individual and the most accurate dose. Thus, theragnostic biomarkers are needed to optimize drug efficacy and diminish toxicity (Hampel and Lista, 2013). They are assumed to have a key position across

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the different phases of AD drug development, from early clinical to late registration trials (Blennow et al., 2014).

Recently, a novel integrated partnership model has been introduced for advancing the field of AD biomarkers from discovery to clinic implementation (O'Bryant et al., 2017). The Food and Drug Administration (FDA)/NIH Biomarker Working Group (FDA-NIH Biomarker Working Group, 2016) released the Biomarkers, EndpointS, and other Tools (BEST) Resource to provide definitions for several terms and concepts, especially analytical validation, candidate surrogate end point, clinical benefit, and the term biomarker itself. In this framework, the biomarker categories recommended are: susceptibility/risk, diagnostic, monitoring, prognostic, predictive, pharmacodynamic/response, and safety. Unfortunately, such distinctions are problematic to implement in AD. For example, amyloid positivity might be designated as a diagnostic or predictive biomarker, or both. However, the distinction between different categories of biomarker are argued to be important in treatment and prevention strategies targeted to individuals' characteristics (FDA-NIH Biomarker Working Group, 2016).

Directions for Alzheimer's disease biomarker research

Substantial progress in discovery, development, and validation of AD-related biomarkers has ushered in a novel era of multimodal investigations, integrating modalities, and different biological fluids (Hempel et al., 2012, 2014; Lista et al., 2015b). Candidate biomarkers have been developed from neurogenetics (Bertram and Hampel, 2011; Hampel and Lista, 2012; Zetsche et al., 2010), from neurochemistry via biological fluids such as blood (plasma/serum) (Henriksen et al., 2014; O'Bryant et al., 2015; Snyder et al., 2014) and CSF (Blennow et al., 2010; Ghidoni et al., 2011), and from structural/functional/metabolic neuroimaging (Chiesa et al., 2017; Ewers et al., 2011; Teipel et al., 2013). The longitudinal dynamics and predictive performances of this multimodal approach have not yet been fully established in terms of sensitivity, specificity, or predictive power (Lista and Emanuele, 2011; Lista et al., 2014). Furthermore, more input from regulatory agencies and industry stakeholders has been recommended (Broich et al., 2011; Hampel et al., 2010a).

Established cerebrospinal fluid biomarkers for Alzheimer's disease

Abnormal CSF concentrations of A β 1-42 peptide, total tau (t-tau), and hyperphosphorylated tau (at the threonine site 181; p-tau181) proteins are considered pathophysiological markers of amyloid pathology, cortical axonal degeneration, and neurofibrillary tangle pathology, respectively. These have been validated as core biomarkers of AD pathophysiology (Frank et al., 2003; Hampel et al., 2008). Several studies have demonstrated that these core biomarkers differentiate AD patients from healthy controls, as well as from patients with other neurodegenerative diseases, including Parkinson's disease and frontotemporal dementia

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(Blennow et al., 2010). Moreover, these three biomarkers distinguish people with MCI due to AD from those with MCI due to non-AD causes, with positive and negative predictive values of above 90% (Hansson et al., 2006; Visser et al., 2009), as well as showing dynamic alterations during preclinical disease stages (Fagan et al., 2014).

The potential diagnostic utility of CSF A β 1-42, t-tau, and p-tau underpins ongoing efforts to standardize biomarker measurements into clinical routine tests where different methodologies are calibrated across clinical settings with high precision. Standardization initiatives include the Global Biomarkers Standardization Consortium (GBSC), Materials and Methods Working Groups (http://www.alz.org/research/funding/global_biomarker_CSF_materials.asp) within the Alzheimer's Association (AA), and the International Federation of Clinical Chemistry and Laboratory Medicine Working Group for CSF Proteins (IFCC-WG-CSF) (<http://www.ifcc.org/ifcc-scientific-division/sd-working-groups/csf-proteins-wg-csf/>). The main aims are to standardize both pre-analytical and laboratory procedures and to harmonize levels between assay formats (Carrillo et al., 2013). Between-laboratory and longitudinal variations are supervised, following the Alzheimer's Association Quality Control Program for CSF biomarkers (Mattsson et al., 2011, 2012). These efforts have encouraged biotech companies to validate upgraded versions of assays and develop CSF biomarker assays on fully automated laboratory analysers. It is thereby hoped that these activities will establish uniform and globally recognized cut-off values for AD CSF biomarkers.

Shifting the focus to developing blood-based biomarkers for Alzheimer's disease

While CSF A β 1-42, t-tau, and p-tau are the most extensively validated biomarkers for the diagnosis of AD, their measurement requires lumbar puncture, which is an invasive procedure potentially associated with adverse effects (e.g. post-procedural headache) and patient discomfort (de Almeida et al., 2011). Although such shortcomings are uncommon in experienced memory clinics (Zetterberg et al., 2010), CSF sampling remains unpopular with clinicians and the public, also due to the necessity of a day-hospital setting. Imaging biomarkers present at least a potential alternative. Such investigations are based on the use of specific radiolabelled ligands capable of binding to fibrillar A β deposits in the brain such as Pittsburgh Compound B (PiB) (Herholz and Ebmeier, 2011). Positron emission tomography with PiB (PiB-PET) has been used to monitor the variations over time in cerebral A β plaque burden, and a significant positive association has been found between PiB binding and histological A β plaque load measured in post-mortem studies (Ikonomovic et al., 2008). Unfortunately, a major limitation of PiB-PET lies in the fact that PiB is labelled with the ¹¹C isotope, which is characterized by an extremely short half-life (approximately 20 minutes). PiB-PET imaging and other more recent radiotracers are therefore costly, time-consuming,

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and unsuitable for routine clinical practice (Klunk and Mathis, 2008; Hampel et al., 2018b).

Because the use of CSF and imaging biomarkers of AD remains chiefly limited to academic research and specialist clinical centres, recent research efforts have focused on identifying and validating potential blood-based biomarkers (Lista et al., 2013b). Importantly, blood collection through venepuncture is less invasive than lumbar puncture. In addition, blood-brain barrier (BBB) disruption, which occurs throughout AD course, may increase the bidirectional exchange of proteins between blood and the CSF (Zipser et al., 2007), potentially providing stage- or endophenotype-specific diagnostic information. Blood-based biomarkers have the potential to be routinely performed both in a primary care setting and in the community, and repeated blood sampling is feasible, even in elderly and frail patients (Thambisetty and Lovestone, 2010). Blood-based AD biomarkers are therefore of increasing interest because of their potential to provide a largely accessible, non-invasive, inexpensive, and easy-to-implement means of supporting diagnosis, treatment stratification, and outcome monitoring (Lista et al., 2013b).

A number of different biomolecules (e.g. proteins, nucleic acids, lipids, and other metabolic products) can be quantified in serum, plasma, or blood cellular compartments (i.e. red blood cells, leucocytes, and platelets). Owing to the diversity of blood-based biological sources of AD biomarkers, they encompass a broad spectrum of different protein concentrations, protein isoforms, and post-translational modifications, as well as numerous metabolic products (e.g. lipids and carbohydrates) and nucleic acids (Thambisetty and Lovestone, 2010). In this regard, microRNAs (miRNA) (a class of non-coding 22-nucleotide-long RNA molecules involved in post-transcriptional modulation of protein expression) (Ha and Kim, 2014) have been recently explored. A few studies have shown that miRNAs can differentiate between AD patients, MCI individuals, and cognitively healthy controls with modest accuracy; however, there are limitations in methodological heterogeneity and miRNA heterogeneity, and there is a need for standardization and validation (Wu et al., 2016). Recently, plasma neurally derived exosomes have been suggested as candidate biomarkers of early AD pathomechanistic alterations (Fiandaca et al., 2015; Goetzl et al., 2015, 2018). It has been reported that: (1) proteins contained in plasma neurally derived exosomes originate predominantly from cellular structures, in contrast with proteins in the CSF and the fluid phase of blood; and (2) protein profiles in plasma neurally derived exosomes in steady-state conditions are thought to reflect those in CNS neurons. For instance, in the case of brain A β accumulation, there is an excellent correlation between levels of brain A β accumulation, assessed through both amyloid PET scans and plasma neurally derived exosomes.

Because of its complexity and multiple interactions with different tissues and organs, blood represents an ideal biological matrix to investigate a large spectrum of molecular networks and pathophysiological

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mechanisms (Issaq, Xiao and Veenstra 2007). However, distinct from the CSF and other body fluids, it must be considered a multifaceted tissue (Thambisetty and Lovestone, 2010).

Neuroproteomics for biomarker discovery

Blood (plasma/serum) has been undoubtedly the most important subject of proteomic studies in the last 15–20 years. The proteome of an organism, as the complement of its genome, is very dynamic and is subject to variations according to cell nature and functional state. Alterations in protein composition are observed in bodily fluids, including blood, and reproduce direct modifications resulting from pathophysiological processes and external stimuli (Apweiler et al., 2009). Proteomics allows the system-wide description of all the proteins in an organism, based on sequence, localization, abundance, post-translational modifications, and biomolecular interactions (Beck et al., 2011). Because of the complexity of the cellular proteome and the low abundance of many physiologically relevant proteins, proteomics presents challenges. As the molecular alterations characterizing the AD brain are all interconnected, a comprehensive exploratory systemic approach is essential to elucidate the pathogenesis and pathophysiology of AD at a complex network level (Kaddurah-Daouk et al., 2013; Noorbakhsh et al., 2009). In this regard, a clear depiction of the significance and role of proteomics in AD pathophysiology is of key relevance.

Use of neuroproteomics and systems biology to understand Alzheimer's disease pathophysiology

As with other neurodegenerative diseases, AD is not limited to the CNS but should be considered as a complex multisystem disease (Lausted et al., 2014). Besides cognitive decline, AD patients may show systemic manifestations (Morris et al., 2014) which can only, in part, be explained by the continuing functional and behavioural impairment associated with neurodegeneration (Rivière et al., 2002). In this respect, the complex and multifaceted manifestations of AD are not limited to the neurological domain, and a systems approach is needed to explore this neurodegenerative disease (Lausted et al., 2014). Moreover, AD is per se a heterogeneous disease in terms of genetic susceptibility, neuropathological underpinnings, and clinical features (e.g. age at onset, severity and type of behavioural and clinical symptoms) (Hampel et al., 2012). Traditionally, the molecular bases of AD pathophysiology have been explored using an a priori approach based on biological candidates informed by current pathogenetic hypotheses.

However, this reductionist approach has failed to capture the complexity of the disease and has not resulted in major therapeutic advances. To circumvent this issue, the unbiased exploratory paradigm of *systems biology*—also referred to as network biology or integrative biology (Castrillo et al., 2018)—has been proposed. This new integrative interdisciplinary framework is chiefly based on the use of multimodal

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high-throughput technological platforms that enable complex networks of biological pathways to be examined simultaneously; the approach can be applied at different system levels, from subcellular compartments to the entire organism (Lista et al., 2016). The key prerequisite to systems biology is an 'all-inclusive' examination and validation of biological data, followed by a thorough statistical analysis, from which new, unbiased pathophysiological hypotheses may stem (Castrillo et al., 2018), based on high-throughput laboratory methods that allow the simultaneous study of a large number of 'omics' markers. Of these, proteomics has been used increasingly in AD.

Proteomics can be defined as a large-scale approach to analyse the identities, quantities, structures, dynamics, and functions of proteins in biological samples (Shevchenko et al., 2015). Besides informing new pathophysiological hypotheses, proteomics biomarkers have been shown to have both diagnostic and prognostic significance (Marko-Varga and Fehniger, 2004). Neuroproteomics is a specific subfield aimed at the molecular and phenotypic analysis of proteins in the CNS and/or CNS-related diseases (Kim et al., 2004), and clinical neuroproteomics seeks to clarify potential diagnostic, prognostic, and monitoring implications (Shevchenko et al., 2015). In 2001, the Human Proteome Organization (HUPO, available at <http://www.hupo.org/>) was launched, with the broad goal of promoting proteomics and its applications in basic research and the clinical field through international cooperation and research collaborations. Under the patronage of HUPO, the HUPO Brain Proteome Project (HUPO BPP, available at <http://www.hbpp.org/>) has been specifically established, with the goal of discovering diagnostic and prognostic biomarkers associated with neurodegeneration and CNS ageing. The ultimate purpose of this initiative is to obtain a better understanding of these conditions and to open new avenues for the development of innovative biomarkers and molecular drug targets.

Overview of the technologies needed for neuroproteomic examination

A major challenge faced by neuroproteomics is the high degree of complexity and heterogeneity of the CNS, which is expressed at both cellular and subcellular levels. This issue may be partially overcome by an optimized and standardized pre-analytical phase, which is a key prerequisite for the identification of clinically useful biomarkers in biological fluids such as blood (plasma/serum). The field of biomarker discovery in neuroproteomics consists of the identification and characterization of proteins and peptides, as well as the detection of significant alterations in their relative/absolute amount/concentration across different pathological conditions (Lista et al., 2017).

Over the last three decades, several technological platforms have been developed to apply the principles of neuroproteomics in biological samples collected from patients with different neurodegenerative diseases (for a detailed methodological review, see Shevchenko et al., 2015). Specifically, currently proteomic approaches are based on the

following sequence: separation, enzymatic digestion (frequently coupled with isotopic labelling), and mass spectrometric analysis (Aebersold and Mann, 2003). In this regard, mass spectrometry is considered the gold standard for the systematic analysis of proteins—from their identification and quantification to the characterization of post-translational modifications and protein-protein interactions. Apart from identification, a protein may truly serve as a candidate biomarker only when it shows specific quantitative or qualitative variations in a specific disease state, as compared with healthy controls (Hampel et al., 2012); in this respect, quantitative neuroproteomics is a research field that aims to quantify the relative and absolute abundance of proteins in two or more conditions (e.g. CNS disease conditions versus apparently healthy individuals or patients undergoing a specific treatment for a CNS disease versus placebo arm). High-throughput platforms and novel high-performance mass spectrometers are currently providing new impetus for this promising research field, and laboratories with up-to-date spectrometry facilities are technically able to characterize, identify, and quantify hundreds of proteins on a daily basis with high accuracy (Castrillo et al., 2018; Lista et al., 2017). An interesting example of ground-breaking technology in the field is the enzyme-linked immuno-mass spectrometric assay (ELIMSA), which combines the sensitivity of mass spectrometry with the high specificity and enzymatic amplification of conventional enzyme-linked immunosorbent assay (ELISA). The key idea of ELIMSA is that the reporter enzymes—horseradish peroxidase or alkaline phosphatase—yield small molecular products that are easily ionizable, making them measurable by ultra-sensitive mass spectrometry and allowing precise quantification of small molecules present at picomolar (10⁻¹² mol) to femtomolar (10⁻¹⁵ mol) levels. This potentially allows measurement over most of the known range of human protein concentrations (Florentinus-Mefailoski and Marshall, 2016; Florentinus-Mefailoski et al., 2014).

It should be emphasized that one of the central benefits of employing proteomics to explore AD and other neurodegenerative diseases is the simultaneous characterization and quantification of hundreds, or even thousands, of proteins (Mann et al., 2013). Basically, proteomic approaches can be divided into explorative and targeted methods. The former makes use of technological platforms with clinical samples to identify specific biomarkers and, consequently, typical pathophysiological molecular signatures that can help fully elucidate the mechanisms responsible for disease progression. The latter is centred on scrutinizing one protein (and its altered forms) or a precise group of proteins. In this context, proteomic methods, coupled with immunopurification and immunoprecipitation protocols, are recurrently used (Brinkmalm et al., 2015).

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The 'multiplex' approach era

Given that the use of individual blood biomarkers has been unsuccessful in defining disease pathophysiology, progression, or diagnosis, a holistic approach is required to elucidate a molecular profile for AD diagnosis. It is therefore critical to understand links between single biomarkers, rather than the outdated approach of studying concentrations of individual candidate biomarkers one at a time. Several analyses have generated sets of biomarkers to differentiate between healthy individuals and AD patients, and assessed a large panel of proteins/peptides in various combinations to yield elevated sensitivity and specificity (Gupta et al., 2013).

Monitoring complex and multifactorial diseases, including AD, involves a large number of analytes, so that optimized treatment strategies are developed (Tighe et al., 2015). Accordingly, integrating novel biomarkers into 'multiplex' immunoassay platforms allows the simultaneous identification and measurement of multiple analytes in a single patient sample. This reduces assay costs, sample volume, and time taken, while simultaneously allowing monitoring of disease progression and outcome prediction, including adverse drug reactions (Tighe et al., 2015). In addition, thanks to the advent of proteomics, multiplex immunoassays can efficiently manage the large amount of data generated, thus accelerating precision medicine and personalized therapies through molecular signatures and biomarker profiles (Hampel et al., 2017, 2018a, b). These, in turn, enable increased diagnostic resolution between strictly associated disease phenotypes, and improved disease monitoring and treatment (Tighe et al., 2015).

At present, several high-content protein microarrays for comparative profiling are commercially available. Nevertheless, only a relatively low number has been certified for *in vitro* diagnostics (IVD) applications. Furthermore, although the capacities of the multiplexing systems are supposed to be elevated, commercially available platforms are only able to utilize a fraction of this potential and seldom handle >20 single analytes (Bastarache et al., 2014; Chowdhury et al., 2009). Notably, suitable algorithms and statistical tools need to be developed and constantly upgraded for managing the massive amount of data generated (millions of assay results per day). It seems likely that currently employed singleplex assays will disappear, in favour of multiplexing immunoassay-based alternatives that offer advantages in terms of assay costs and time. Furthermore, multiplexing provides more complete analysis for performing differential diagnoses and monitoring of therapeutic interventions (Tighe et al., 2015).

Blood (plasma/serum) biomarkers for Alzheimer's disease

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Blood-based markers of amyloid pathophysiology

Several efforts have been focused on discovering and developing diagnostic biomarkers for AD in peripheral blood (Lista et al., 2013b; Snyder et al., 2014).

It is well documented that cerebral A β enters the peripheral circulation through the BBB. Several molecular transporters—including, for instance, the receptor for advanced glycation end products (RAGE) and the low-density lipoprotein receptor-related protein (LRP)—regulate the rate of efflux from the CNS into the plasma. It is well acknowledged that the peripheral (i.e. blood) concentration of A β peptides reflects the brain deposition of A β in both healthy and pathophysiological conditions (Roberts et al., 2014).

The dynamics of plasma have a time-dependent fashion similar to that of the CSF; indeed, longitudinal studies have reported that plasma A β alterations show a peak during the early stages of AD and a plateau, or even a slight decrease, during disease progression (Mayeux et al., 2003).

A β monomers are the most investigated surrogate markers of AD-related brain A β accumulation in blood (plasma/serum), both as cell-bound and as cell-free circulating molecules. However, the extent to which blood A β concentrations accurately reflect the occurrence of extracellular aggregation and accumulation of A β is not yet fully elucidated (Wang et al., 2017). Studies aimed at comparing the diagnostic performance of plasma A β with other measures of brain A β deposition have increasingly been implemented to identify individuals at risk of AD, for which a non-invasive, accessible, and less expensive investigation might be more suitable, especially in contexts-of-use involving large-scale populations and several time series.

To date, only one meta-analysis has been carried out to determine whether plasma A β concentrations may predict the development of dementia (either of AD *spectrum* or not) and MCI. Koyama and colleagues (2012) identified 13 studies exploring the accuracy (combination of sensitivity and specificity) of plasma A β_{1-42} and A β_{1-42} /A β_{1-40} ratio in predicting dementia, including AD and cognitive decline (Koyama et al., 2012). The authors showed that a reduction in plasma A β_{1-42} /A β_{1-40} ratio is strongly associated with an overall higher risk ratio for developing AD. Thus, besides a robust biological rationale, plasma A β_{1-42} /A β_{1-40} (in some cases A β_{1-40} /A β_{1-42}) ratio has been reported to have a relevant clinical significance as a reliable predictor of A β cerebral deposition (Koyama et al., 2012). Indeed, in the last 5 years, many studies have shown a good diagnostic accuracy of plasma A β_{1-42} , and even more so A β_{1-42} /A β_{1-40} , with a widely accepted overlap in sensitivity and specificity between the CSF and plasma A β markers and between the latter and A β PET imaging (Janelidze et al., 2016; Ovod et al., 2017; Teunissen et al., 2018).

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In particular, a growing body of analyses has assessed the strength of the association between plasma A β and A β PET imaging (rather than the CSF) using both a dichotomized status (positivity or negativity to A β) and quantitative measures such as the standardized uptake value ratio (SUVR). Interestingly, Nakamura and colleagues reported that the A β_{1-40} /A β_{1-42} ratio presented an accuracy of approximately 90% when using A β PET imaging as a gold standard in two pooled cohorts (either combined or alone) of cognitively normal, prodromal, and dementia-stage AD participants (Nakamura et al., 2018). In a study conducted in the Australian Imaging, Biomarker and Lifestyle (AIBL) Flagship Study cohort, Fandos and colleagues (2017) showed that the total protein A β_{1-42} /A β_{1-40} ratio reached 81% positive predictive value for high cortical A β burden (Fandos et al., 2017). Further longitudinal studies are needed since, although the overall scenario is encouraging, a substantial amount of the literature is controversial. As a result, standardization of plasma A β peptides both for clinical and pharmacological use, e.g. for clinical trial outcome measures, has not yet achieved a definitive approval, and international consensus is still missing on normal cut-off values for plasma (and even CSF) A β peptides. Despite scientific agreement on A β as a biofluid surrogate marker of cerebral pathophysiological mechanisms, the current lack of thresholds prevents plasma A β from attaining a definitive standardization for clinical practice and pharmacological trials.

Discrepancies emerging from plasma studies are the same as for the CSF and might be attributable to the high degree of between-site and intra-site variability, as well as to analytical and methodological differences such as the assay utilized and its detection limit. Furthermore, most of the investigations lack a reliable healthy control group, since the main inclusion and exclusion criteria are represented by clinical measures, and not by biological signatures of AD, such as imaging evidence of brain A β accumulation. In addition, several clinical and demographic confounding factors are not considered—namely, participants' age and sex, medical comorbidities and concomitant drugs, lifestyle (i.e. diet, physical activity, and sleep-wake cycle), and habits (i.e. caffeine, tobacco, and alcohol intake).

Whether plasma A β can be a predictor of cognitive decline, including AD, needs to be better investigated. For instance, plasma A β concentrations reported from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort exhibited a very low correspondence to clinical state (Toledo et al., 2011). However, it is important to highlight that such findings may not be related per se to the assessment of plasma A β since the overall pathophysiological brain A β accumulation and its progress over time have not been identified yet as direct and unequivocal predictors of future cognitive decline and disease progression.

Besides the most investigated A β monomeric species (A β_{1-42} and A β_{1-40}), other A β monomers are potentially useful. Interestingly, the A β_{1-17} monomer has exhibited a good predictive value for brain A β deposition. Thus, A β_{1-17} is a promising candidate as a diagnostic biomarker of AD. In

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one study, the ratio of free to cell-bound $A\beta_{1-17}$ in blood distinguished between healthy controls and people with MCI or mild AD, with high rates of diagnostic performance (Perez-Grijalba et al., 2015). Other novel $A\beta$ isoforms are of potential usefulness as target engagement biomarkers and for monitoring the biochemical effect of an experimental treatment. For instance, in a clinical trial of the γ -secretase inhibitor semagacestat (LY450139), an increase in CSF concentrations of short $A\beta$ isoforms was found, showing a dose-dependent fashion. In the same study, there was no significant effect on plasma $A\beta$ or CSF $A\beta_{1-42}$ or $A\beta_{1-40}$ (Portelius et al., 2010). Several platforms have been developed to assess blood (plasma) $A\beta$ concentrations. In this regard, Araclon Biotech Ltd (Zaragoza, Spain) developed two ELISA sandwich colorimetric tests to assess plasma $A\beta_{1-42}$ and $A\beta_{1-40}$, in order to measure—directly and indirectly (i.e. through calculation)—biomarkers related to an increased probability to develop prodromal AD (Perez-Grijalba et al., 2013, 2016). Other ELISA-based immunoassays and novel methodologies are under development. An emergent methodology is represented by immunoprecipitation-mass spectrometry that was used in a recent analysis by Nakamura and colleagues (Nakamura et al., 2018).

This significant heterogeneity highlights the need for further longitudinal investigations aimed at assessing whether plasma $A\beta$ may be introduced into clinical practice as a biomarker (perhaps even preclinical) of $A\beta$ pathophysiology. Of note, the different analytic approaches have different costs in terms of devices, operator expertise, and data-processing time.

The biological mechanisms underlying the dynamic changes of $A\beta$ metabolism arise from a complex cross-talk among neurons, immune cells, BBB components, and peripheral tissue. Indeed, it has already been shown that $A\beta$ metabolism undergoes significant physiological changes over time, i.e. both in ageing and diseases (Wang et al., 2017). Thus, another key point along the road to standardization of plasma $A\beta$ for clinical practice and pharmacological trials will be to accomplish a full understanding of the dynamics regulating $A\beta$ metabolism at a system level: rates of active transportation across the BBB and glymphatic systems, brain outflow kinetics, and rates of vascular, immune, and peripheral tissue turnover (i.e. liver and kidney). This will provide researchers with a minimally invasive, simple, and versatile blood test, useful for stratification of risk for preventive interventions and biological screening for clinical trial protocol inclusion, as well as routine diagnostic, and potentially even prognostic, work-up.

β -site amyloid precursor protein-cleaving enzyme 1

The APP cleaving enzyme—called β -site APP-cleaving enzyme 1 (BACE1)—is an aspartyl protease playing a key role in modulating $A\beta$ processing. It cleaves APP in its ectodomain, generating the amino-(N) terminus of $A\beta$ and the membrane-bound carboxyl-terminal fragment C99 from which γ -secretase will generate neurotoxic $A\beta$ monomers and oligomers. BACE1 is assumed to have a pivotal role in regulating presynaptic activities.

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Besides leading to the production of toxic A β fragments, BACE1 overexpression (potentially even blockade) may result in dystrophic axonal neurites, with subsequent loss of plasticity. Thus, BACE1 is a key candidate drug target for AD, even during the preclinical stages. BACE1 inhibitors have been reported to have therapeutic and disease-modifying effects in AD animal models, by slowing down progressive cerebral A β deposition (Hampel and Shen, 2009). However, despite a strong rationale, clinical drug development trials targeting BACE1 in humans have failed to accomplish primary end points. A possible explanation could be the current lack of fluid biomarkers for target engagement (expression and activity of the enzyme). Data on CSF BACE1 concentrations in early stages of AD are becoming increasingly robust, as previously reviewed (Hampel and Shen, 2009; Hampel et al., 2010b).

Since BACE1 potentially appears to be an excellent biomarker for several contexts-of-use, as it directly reflects a pathophysiological process, its validation in plasma would represent a unique possibility to peripherally access AD. So far, one study has investigated the role of peripheral BACE1 expression and activity in healthy controls, people with MCI (either converters or non-converters to subsequent AD), and patients with AD (Shen et al., 2018). The authors found that MCI converters and AD patients had significantly higher BACE1 activity and expression, compared to healthy controls and MCI non-converters, with a gradient towards AD. Compared with healthy controls, BACE1 activity was increased in MCI non-converters, MCI converters, and AD patients. A sex effect on BACE1 activity was also observed since women exhibited higher activity and expression, compared to men, in MCI non-converters, MCI converters, and AD patients. These data are in line with those from AD post-mortem analyses (Nyarko et al., 2018) and should be considered in upcoming studies on this marker.

Longitudinal investigations, including larger sample size and time series, are required to assess whether increased plasma BACE1 concentrations and activity are a predictive surrogate outcome of cognitive impairment and neurodegeneration in asymptomatic individuals at risk of AD. This, in turn, will allow the depiction of different longitudinal molecular trajectories.

Tau protein

Tau is a microtubule-associated protein essential for the whole cellular cytoskeletal stabilization. N-terminal truncation and hyperphosphorylation of tau has a detrimental effect on the physiological activity of the protein, as well as on neuronal homeostasis. Consequently, the progressive accumulation of aberrant phosphorylated strains leads to widespread deposition of neurofibrillary tangles and threads (i.e. neurofibrillary pathology), which cause loss of dendritic spine density and, ultimately, neuronal cell death (Braak and Del Tredici, 2015). Current diagnostic research criteria for AD include CSF t-tau and hyperphosphorylated tau at Thr181 site (p-tau₁₈₁) as established markers

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reflecting neurodegeneration and neurofibrillary pathology, respectively (Dubois et al., 2014).

A novel ultra-sensitive assay for tau protein in peripheral blood has recently been developed based on digital array technology and consisting of previously validated digital standard ELISAs transferred onto the single molecule array Simoa™ platform. This methodology significantly improves analytical sensitivity and allows for the ultra-sensitive (sub-femtomolar range) and accurate detection of tau in plasma (Zetterberg et al., 2013). Of note, no assay has been currently validated for the plasma measurement of hyperphosphorylated tau strains. Thus, given that peripheral assessment of a surrogate marker of neurofibrillary pathology (i.e. neurofibrillary tangles) is not possible, 'peripheral' screening, diagnosis, and risk stratification of AD-related pathophysiological mechanisms remain limited to brain A β accumulation.

Zetterberg and colleagues (2013) were the first to assess plasma t-tau concentrations in a pooled cohort of clinically identified healthy control, MCI, and AD participants, and they reported higher concentrations of plasma t-tau in AD, compared to controls and MCI (Zetterberg et al., 2013). Notably, participants with MCI converting at follow-up did not show significant differences in terms of t-tau values, when compared with non-converter MCI patients and healthy controls, raising the question of whether plasma t-tau is appropriate as an AD diagnostic/prognostic indicator.

Mattsson and colleagues cross-sectionally scrutinized the diagnostic value of plasma t-tau within the ADNI and BioFinder cohorts and found, in the former cohort, more elevated plasma t-tau concentrations in AD dementia patients, compared to healthy controls and MCI patients. They also found, in the ADNI cohort, that higher plasma t-tau concentrations were associated with worse cognition, lower CSF A β ₁₋₄₂, higher brain atrophy, and higher brain hypometabolism. In addition, in the BioFinder cohort, all individuals showed a weak association between plasma t-tau concentrations and AD CSF core biomarkers, including CSF t-tau and p-tau₁₈₁. Therefore, despite group-level differences, the data did not substantiate plasma t-tau as an AD diagnostic biomarker but suggested its potential role as a predictor of neurodegeneration and clinical worsening (Mattsson et al., 2016).

A recent population-based cohort study explored the utility of plasma t-tau as a prognostic marker for cognitive decline and dementia without reaching a firm conclusion. Elevated plasma t-tau concentrations were associated with the degree of cognitive impairment; however, in line with previous studies, the results showed heterogeneity according to clinical status (healthy controls, MCI, AD) and duration of clinical follow-up (Mielke et al., 2017).

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In a recent multimodal study, Deters and colleagues reported, in a pooled cohort of healthy controls and people with MCI and AD, that plasma t-tau correlated with the rate of overall and regional grey matter density, irrespective of the clinical condition, thus confirming that plasma t-tau may reflect brain neuronal loss, regardless of upstream pathophysiological processes (Deters et al., 2017). Indeed traumatic brain injury, Creutzfeldt-Jakob disease, stroke, and other neurodegenerative disorders (non-AD) show different patterns of increased plasma t-tau concentrations (according to the pathophysiological process underlying the disease), when compared with the healthy condition (Zetterberg, 2017).

In summary, plasma t-tau concentrations are significantly increased only in the late prodromal or dementia stage of AD, thus substantially restricting the utility of this marker for diagnostic purposes during the preclinical stages. However, some studies have shown a correlation between plasma t-tau and neurodegeneration markers, thus suggesting to further explore whether plasma t-tau may serve as a prognostic indicator. On the flip side, many studies have indicated there is no significant correlation between plasma t-tau and CSF t-tau—an established biomarker of AD-related neurodegeneration. This suggests that peripheral metabolism of t-tau may undergo changes that are irrespective of the CNS processing and clearance of the protein, limiting the potential of plasma t-tau as a marker of AD.

Regarding p-tau₁₈₁, a semi-sensitive assay for tau hyperphosphorylated at Thr181 (similar to the most employed CSF test) with electrochemiluminescence detection has been developed (Mielke et al., 2018). Using this assay, plasma p-tau₁₈₁ concentration was higher in AD dementia patients than in controls, and moreover, plasma p-tau₁₈₁ concentration was associated with global SUVRs of both Aβ- and tau-PET. A very recent post-mortem study (Park et al., 2019) demonstrated that plasma tau-related biomarkers (both total t-tau and p-tau₁₈₁) are significantly correlated with brain tauopathy (i.e. tau Braak stages) and predict tau-PET status (either positive or negative).

Blood-based molecular profiles for Alzheimer's disease

Various studies have investigated the existence of a definitive molecular profile, i.e. a specific set of blood (plasma/serum) proteins/peptides of diagnostic usefulness for AD. Some relevant examples are summarized here.

- One of the most significant analyses was performed by Ray and colleagues (2007), who exploited protein array technology (cytokine antibody arrays) to scrutinize 120 secreted cell-signalling proteins in plasma samples of AD patients and controls without dementia. Notably, a set of 18 signalling plasma proteins was able to discriminate AD from control individuals, with nearly 90% accuracy, and identified MCI individuals converting to AD within 2 years, with 81% accuracy

(Ray et al., 2007). Biological examination of the 18 selected plasma proteins indicated: (1) a global decrease in the number of factors related to haematopoiesis and inflammation; and (2) deficiencies associated with neuroprotection, neurotrophism, phagocytosis, and energy homeostasis. The 18 analytes were represented by cytokines, chemokines, and growth factors, all belonging to a molecular network by which cells communicate each other. This was referred to as the 'cellular communicome'. Proteome Sciences plc developed a quantitative mass spectrometry-based assay to define a panel of nine candidate plasma proteins (O'Brien et al., 2008). Interestingly, Soares and colleagues (2009) verified the reproducibility of a subset of the original set of 18 markers previously characterized by Ray and colleagues (2007) using the Luminex xMAP® technology (Luminex Corporation, Austin, TX, USA) (Ray et al., 2007). The diagnostic accuracy using the subset was 61%. However, a subsequent multivariate analysis of an 89-analyte panel provided a diagnostic accuracy of 70%, suggesting a potentially useful plasma-based AD molecular signature as a screening tool (Soares et al., 2009).

- O'Bryant and colleagues (2010) established an algorithm based on a set of 30 serum proteins, generating a risk score with 80% sensitivity and 91% specificity for detecting AD (O'Bryant et al., 2010). This group of proteins—encompassing several inflammatory and vascular markers—showed an elevated level of diagnostic accuracy in AD, similar to that of CSF studies; moreover, this algorithm correlated with neuropsychological test performance when tested in combination with clinical and demographic data (O'Bryant et al., 2011).

- Another blood-based biomarker panel, based on multivariate data analysis, discovered three biomarkers—cortisol, von Willebrand factor, and oxidized low-density lipoprotein antibodies—that differentiated early AD patients from cognitively healthy controls, with over 80% accuracy (Laske et al., 2011).

- A gel-based proteomics approach performed in a cohort of AD, MCI, and cognitively normal individuals indicated a set of five analytes involved in complement activation and coagulation—component C3, component C3a, complement factor-I, γ -fibrinogen, and α -1-microglobulin—that, in conjunction with age and sex, accounted for >35% of variance of whole brain volume in AD patients (Thambisetty et al., 2011).

- An analysis from the Biomarkers Consortium Alzheimer's Disease Plasma Proteomics Project assessed a set of plasma analytes via a multi-analyte profile (MAP) panel (Human Discovery MAP version 1.0; Myriad RBM, Austin, TX, USA) and the Luminex® 100™ system (Luminex Corporation, Austin, TX, USA). This panel of plasma proteins showed some overlap with the CSF and an association with the *APOE* ϵ 4 allele. Specifically, increased concentrations of eotaxin 3, pancreatic polypeptide, and N-terminal protein B-type brain natriuretic peptide were reported in AD patients and MCI individuals, thus corroborating similar alterations found in CSF samples in AD and MCI. Increased

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concentrations of tenascin C and decreased concentrations of immunoglobulin M (IgM) and apolipoprotein E (APOE) were also detected (Soares et al., 2012).

- A multivariate analysis of 146 plasma analytes in a cohort of AD patients, MCI individuals, and cognitively normal older individuals from the ADNI database indicated four different molecular signatures discriminating AD from controls (sensitivity and specificity between 74% and 85%). The four molecular profiles shared five biomarkers: apolipoprotein A-II, APOE, serum glutamic oxaloacetic transaminase, α -1-microglobulin, and brain natriuretic peptide. However, none of the analytes predicted progression from MCI to AD during a 12- and 24-month follow-up (Llano et al., 2013).
- A list of 21 blood proteomics-based analyses of AD was revised and led to 163 candidate analytes. Interestingly, four biomarkers linked to AD-related phenotypes were consistently found in five independent cohorts: α -1-antitrypsin, α -2-macroglobulin, APOE, and complement C3. A large-scale replication study selecting 94 plasma analytes out of the 163 candidates was performed in 677 participants from the AddNeuroMed (ANM) and the Alzheimer's Research UK/Maudsley BRC Dementia Case Registry at King's Health Partners (ARUK/DCR) cohorts using the SOMAscan[®] Proteomic Assay (SomaLogic Inc., Boulder, CO, USA). Nine out of the 94 candidates were associated with AD-related phenotypes and showed sufficiently satisfactory replication to be included in additional analyses. This finding indicates that AD pathophysiology influences the blood proteome with a certain degree of consistency (Kiddle et al., 2014).
- An analysis conducted in three multicentre cohorts of AD patients, MCI individuals, and cognitively healthy older people used the Luminex xMAP[®] technology (Luminex Corporation, Austin, TX, USA) to validate a prior set of plasma biomarkers associated with AD. Sixteen analytes correlated with cognitive decline and disease severity. In particular, MCI individuals showed the most significant associations, with a set of ten plasma proteins predicting progression to AD (sensitivity 85%, specificity 88%, and accuracy 87%). These biomarkers might be potentially useful to select patients for clinical trials and assess individuals with subjective memory complaints (Hye et al., 2014).
- A study using the iTRAQ-labelled proteomics technique reported a set of plasma analytes associated with early pathophysiology by examining their alterations at both asymptomatic and symptomatic stages of autosomal dominant AD. After comparing 81 proteins across asymptomatic and symptomatic mutation carriers, as well as related non-carriers, minor alterations were found at the asymptomatic stage versus the symptomatic stage, with plasma concentrations of seven and 16 proteins significantly changed in asymptomatic and symptomatic mutation carriers, respectively. The analytes were represented by complement components C3, C5, and C6, apolipoproteins A-I, A-IV, C-I, and M, histidine-rich glycoprotein,

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heparin co-factor II, and attractin, which play a role in inflammation, lipid metabolism, and vascular health. Further inspections are necessary to validate this molecular profile (Muenchhoff et al., 2016).

- A recent investigation inspected serum biomarkers in a Han Chinese population via an unbiased iTRAQ approach. After discovering 22 differentially expressed analytes, nine potential markers were further validated. In particular, for the first time, alterations in serum concentrations of zinc- α -2-glycoprotein, fibulin-1, platelet basic protein, thrombospondin-1, S100 calcium-binding protein A8, and S100 calcium-binding protein A9 were observed in AD patients, compared to healthy controls. Since the data emphasized the role of A β metabolism and blood coagulation in AD pathophysiology, proteins associated with these two processes might represent peripheral blood indicators for AD (Shen et al., 2017).

Since it is clear that blood proteins are subject to variations in AD individuals, a blood biomarker for AD diagnosis should be plausible, particularly since promising biomarkers for AD diagnosis—A β peptides and proteins linked to inflammatory mechanisms—are not brain-specific but are commonly detected in the periphery and may undergo alterations following the progression of AD (Lista et al., 2013a,b).

Presently, however, there are no proteins (either transcripts or metabolites) in blood that have been acceptably replicated as AD biomarkers. Moreover, based on the literature, it seems arguable that a single plasma/serum marker alone will not be sufficient for diagnostic purposes. Instead, developing a combination of biological markers—i.e. a set of proteins combined with other blood-based, or even non-blood-based, markers (as neuroimaging markers)—appears as the most reasonable diagnostic strategy. However, it is still uncertain whether a unique molecular profile for AD will be identified that will satisfy multiple purposes. Rather, it is expected that there will be different sets of biomarkers for: (1) supporting AD diagnosis; (2) predicting AD outcome or conversion from MCI; and (3) monitoring disease progression (Thambisetty and Lovestone, 2010). More technical questions, such as whether, for instance, it is better to use mass spectrometry, rather than antibody arrays or another methodological platform/approach, are relatively unimportant. What is really crucial is how to use the components of all these approaches in combination (Lovestone, 2014).

In conclusion, there is evidence suggesting that the scenarios for identifying and validating blood-derived markers for early diagnosis of AD and prognosis are encouraging (Henriksen et al., 2014). This is highlighted by the recent formation of the Blood-Based Biomarker Interest Group (BBBIG), a key international working group of leading AD scientists from academia and industry, aiming at establishing global standards and best practices for the appraisal of blood-based biomarkers. In addition, a Professional Interest Area focused on Blood-Based Biomarkers (BBB-PIA), as a part of the Alzheimer's Association's

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International Society to Advance Alzheimer's Research and Treatment (ISTAART), has been created to support the harmonization process of pre-analytical and analytical protocols and to emphasize the need for a biorepository of clinical reference samples, enabling not only assay harmonization, but also the assessment of clinical performance (Henriksen et al., 2014; Snyder et al., 2014). International collaborations between academia and industry are key to accelerate the development of blood-based biomarkers and to avoid the limitations/challenges of CSF and imaging. To this end, the Alzheimer's Association ISTAART and BBB-PIA will facilitate collaborative efforts to accelerate progress in the AD blood-based biomarkers field (Henriksen et al., 2014; Snyder et al., 2014).

Challenges in searching for blood protein biomarkers

Blood, on the one hand, represents an invaluable source of biomarkers but, on the other hand, is not without shortcomings, and the quest for blood-based protein biomarkers poses major challenges. One challenge is the high degree of peptide and protein diversity. In this regard, post-translational modifications, amino acid side chain modifications, and different cleavages of the polypeptide chains generate a number of different protein isoforms in the plasma/serum proteome (Anderson and Anderson, 2002). A second challenge is the high level of variation in the range of plasma/serum protein concentrations (encompassing 10^{11} – 10^{12} orders of magnitude, from mg/mL to pg/mL) (Anderson and Anderson, 2002). Thirdly, approximately ten of the high-abundance proteins (HAPs) represent roughly 90% of the total protein mass in human plasma/serum: albumin (which alone represents approximately 50% of all plasma/serum proteins), immunoglobulins, transferrin, fibrinogen, α -2 macroglobulin, α -1 antitrypsin, C3 complement factor, and haptoglobin (Lista et al., 2013a). Unfortunately, HAPs cannot be considered informative as disease biomarkers, so potential biomarkers have to be sought in the remaining 10% of proteins, which are a complex mixture of highly heterogeneous middle- and low-abundance proteins (LAPs). However, these potential biomarkers are 'masked' by the presence of HAPs and are sometimes referred to as the 'hidden proteome' (Boschetti et al., 2007) (Fig. 6.1). In general, disease biomarkers vary in concentrations from ng/mL to pg/mL (Burtis et al., 2001). As a result, separation or removal of HAPs is paramount to enable us to identify and quantify most protein species in a biological sample.

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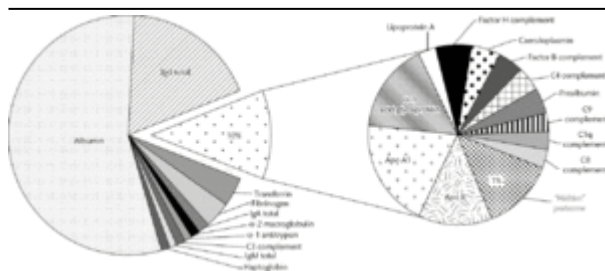


Fig. 6.1

A significant portion of the total protein content in plasma and serum is comprised of just a few proteins. Given that the plasma/serum proteome should contain a rich, unexploited source of disease-specific diagnostic information, the analysis of such biological fluid is particularly important when considering clinical questions. Unfortunately, plasma and serum include a narrow population of different high-abundance proteins (HAP). The ten most abundant proteins represent approximately 90% of the total protein content in human plasma/serum; the 22 most abundant proteins are supposed to embrace about 99% of the total protein mass. As a result, the tens of thousands of other different proteins and peptides, that should encompass all possible biomarkers of diseases, result to be buried and hidden under such few predominant HAP. The 'hidden proteome' expression refers to the low- and very low-abundance proteins (LAP). They constitute less than 1% of the total protein content.

HAP, high-abundance proteins; LAP, low-abundance proteins; IgA Total, Immunoglobulin A Total; IgM Total, Immunoglobulin M Total; Apo A1, Apolipoprotein A1; Apo B, Apolipoprotein B.

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Owing to the wide concentration range and the inherent complexity of proteins (compared with other biological molecules), current proteomic technologies are able to investigate only a fraction of all dynamic biomarker-relevant changes that occur under different pathophysiological conditions (Thambisetty and Lovestone, 2010). However, novel strategies have been introduced, such as the untargeted ModifiComb approach to the analysis of post-translational modifications (Savitski, Nielsen and Zubarev 2006) and the SpotLight approach to the analysis of the 'hidden proteome' in blood that includes a simple enrichment step for polyclonal immunoglobulin G (Lundstrom et al., 2017).

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Pre-analytical and analytical bias

There are many pre-analytical and analytical sources of bias for blood protein biomarkers that may affect their future clinical applicability, as well as current research use; they are summarized in Box 6.1. Pre-analytical variables may affect the quality of the samples under scrutiny and subsequent data quality and can be broadly distinguished into two categories: technical (originating from sample collection, processing, and storage) and biological (deriving from intrinsic features of the individuals from whom the sample is drawn, i.e. age, sex, ethnicity, and lifestyle) (Ferguson et al., 2007).

Box 6.1 Types of pre-analytical and analytical bias

Preanalytical bias, preceding the point of actual sample analysis, can be dichotomized into technical or biological.

Analytical bias arises from discrepancies concerning sample-processing procedures, i.e. how samples are investigated.

Pre-analytical bias

Technical variables

- Blood derivatives (plasma versus serum)
 - Plasma: incubation time preceding separation of plasma from blood cells
 - Serum: clotting procedures
 - Serum: clotting time prior to preparing serum
- Sample handling procedures
 - Plasma: nature of anticoagulant (heparin, EDTA, citrate)
 - Plasma: adequate filling of the tubes during collection
 - Plasma: platelet contamination and activation
 - Serum: peptides resulting from coagulation events
 - Serum: peptides resulting from enzymatic activities
 - Serum: release of peptides from the blood clot
- Sample collection mode
 - Preparation of blood collection site (avoiding haemolysis)
 - Site of venepuncture (median cubital vein)
 - Way of collecting samples
 - Position of the patient (standing, lying, sitting)
 - Tourniquet application and needle bore size

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- Venous occlusion time length
- Collection tubes
 - Spreading of substances released from collection tubes
 - Silicones
 - Polymeric surfactants (PVP, PEG)
 - Clot inhibitors or activators
 - Polymeric gels in serum separator tubes
 - Rubber stoppers and plastics covering tube walls
 - Adsorption of serum/plasma proteins to tube walls
 - Red-top tubes
 - Serum separator tubes
- Temperature
 - Temperature for collection and transport practices within and between facilities
 - Short-term storage temperature (hours/days)
 - Long-term storage temperature (months)
 - Number of freeze-thaw cycles
- Protease inhibitor addition
 - AEBSF

Biological variables

- Immutable factors
 - Age, gender, and ethnicity
 - Genetic polymorphisms
- Potentially modifiable factors
 - Lifestyle factors
 - Diet
 - Obesity
 - Alcohol consumption
 - Smoking
 - Physical activity

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Analytical bias

- Sample-processing procedures
 - Liquid-handling methods (manual or robotic)
 - Buffer composition and sample dilution
 - Depletion of HAPs
 - Centrifugal ultrafiltration
 - Solid-phase extraction
 - Organic solvent extraction
 - Enrichment of LAPs
- Peptide ligand libraries
 - Plasma/serum desalting
 - Fractionation
 - Electrophoresis
 - Liquid chromatography
- Experimental protocols
 - Sample pH
 - Dilution factors
 - Chemistry of arrays
 - Amount of sample loaded onto the array/plate
 - Position of the sample on the array/plate
 - Sample binding/washing/drying methods
 - Type of matrix used
 - Instrument settings
 - Mass spectra acquisition settings
 - Energy and number of laser shots
 - Environmental factors (temperature, humidity)

AEBSF, 4-(2-aminoethyl)-benzenesulfonyl fluoride; EDTA, ethylenediaminetetraacetic acid; HAP, high-abundance protein; LAP, low-abundance protein; PEG, polyethylene glycol; PVP, polyvinylpyrrolidone.

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Discrepancies in procedures used for sample processing are the main source of analytical bias. These factors can exert major effects not only on the outcomes of a biomarker discovery study, but also on the subsequent validation phase. Proteomic studies are not conducted on whole blood, but on plasma and/or serum. Plasma is the liquid portion of blood that suspends cells such as red blood cells, leucocytes, and platelets, and it may be isolated from whole blood by centrifugation at low speeds in the presence of an anticoagulant (Issaq et al., 2007). Serum is plasma with clotting factors (e.g. fibrinogen) removed, and therefore can be isolated by allowing blood to clot (without any anticoagulant) before centrifugation. During the coagulation process for serum preparation, the concentrations of some proteins in the sample are altered and also protein fragments are released by platelets and other cells. The absence of most fibrinogen content makes serum protein concentrations lower than those in plasma. Other proteins may also be removed as a result of specific or non-specific interactions occurring inside the fibrin clot (Issaq et al., 2007).

The issue of proper selection of the optimal specimen (i.e. plasma versus serum) for proteomic studies has been thoroughly discussed (Hanash, 2012; Lista et al., 2013b). In any case, standardization is expected to be difficult, owing to the large number of variables in need of systematic study (Tuck et al., 2009). Ideally both sample types—plasma and serum—should be collected and analysed simultaneously.

Towards a blood-based model for patient screening and precision medicine therapeutics

The great majority of biomarkers currently in use to confirm the clinical diagnosis of AD are biochemical markers measured in the CSF and/or imaging biomarkers (e.g. obtained from PET imaging scans). Because such markers fail fully to capture the marked heterogeneity of AD pathophysiology, future efforts should be tailored at developing and validating a multi-tiered, multi-marker model. However, a major challenge will be the identification of an early inexpensive marker that may be used to screen for preclinical AD in a primary care setting. When available, such a marker would be invaluable to identify specific subgroups of high-risk individuals in need of more expensive (e.g. PET imaging) or invasive (e.g. CSF sampling) second-level diagnostic modalities. Accordingly, imaging/CSF screening is presently unfeasible in a general population setting, because of high costs of brain imaging and/or ethical limitations to lumbar puncture. Simple, non-invasive screening tools are therefore eagerly awaited (O'Bryant et al., 2016). Ideally, a screening test for AD in a real-world, primary care setting should be: (1) blood-based (i.e. simple, scalable, and not invasive); and (2) able to identify people who should not undergo second-level diagnostic assessment (because of the large number of disease-positive individuals). Current epidemiological data indicate that approximately 12% of people aged >65 years may have AD (Alzheimer's Association, 2016). If we estimate that approximately 20% are affected by any neurodegenerative disease in this age group, then

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approximately 80% are disease-negative. A cost-effective multi-tiered approach therefore should initially be able to exclude the highest possible number of disease-negative people. This would require a 90% negative predictive value, regardless of the positive predictive value (which is 20% or less for primary care tools) (O'Bryant et al., 2017). A primary care screening modality should be an imperative as soon as disease-modifying therapies become available, since effective screening will result in a markedly increased number of high-risk individuals in the general population who will seek prevention or treatment of AD. In addition, the availability of disease-modifying drugs will undoubtedly require patients to test positive on blood screening tools for subsequent referral to second-level tests (e.g. PET imaging and/or CSF sampling) for confirmation.

The economic implications of primary care screening merit comment. On the basis of a \$100 fee for a single AD blood test, the total cost for screening only 20 million people would be as high as \$2 billion. Using a 20% expected prevalence, and under the assumption of 80% sensitivity and 75% specificity, the resulting positive predictive and negative predictive values would be 48% and 93%, respectively. In a scenario in which 20 million people are screened, the results would be as follows: (1) 14,900,000 people would be excluded from second-level tests (of whom 500,000 would be false-negative); and (2) 5,100,000 individuals would be judged as in need of CSF sampling and/or PET imaging. With the cost for a single PET scan being \$5,000, the resulting financial burden for second-level PET imaging would total \$25 billion. However, the availability of a blood screening test in primary care would avoid PET imaging in nearly 15 million individuals, resulting in annual savings as high as \$73 billion. Such figures would be even higher when we consider that the total number of people aged ≥ 65 years worldwide was >600 million in 2016. These calculations simulate the major impact that blood-based screening of AD and the availability of disease-modifying therapies might have in the next few decades.

Another major implication of AD blood-based biomarkers concerns the implementation of the precision medicine paradigm for the treatment and prevention of neurodegenerative diseases (Hampel et al., 2016, 2017, 2018a,b). Specifically, such markers may be helpful in identifying specific subgroups showing different dysfunctions in key biological systems. Previous studies have shown the clinical utility of neuroproteomics in the discovery of new neurodegenerative disease biomarkers (Henchcliffe et al., 2011; Ho et al., 2011) in an unbiased fashion (i.e. not informed by current pathophysiological models). For instance, neuroproteomics highlighted the potentially prominent role played by neuroinflammation in the pathophysiology of AD and other neurodegenerative disorders (Durrenberger et al., 2015; Heneka 2014), leading to the hypothesis that neuroinflammatory mechanisms are paramount in AD pathogenesis, at least in a subset of patients. In this specific subgroup, the pathogenetic role of A β peptides, tau protein, and α -synuclein may be less prominent

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than originally expected. We may therefore delineate a scenario in which blood-based biomarkers are a prerequisite to CSF analysis and/or PET imaging; further profiling may be subsequently utilized to implement multi-model interventions targeted at specific patient subgroups (Fig. 6.2) within the precision medicine framework (Baldacci et al., 2018).



Fig. 6.2

Schematic depiction of multi-level biomarker-driven diagnostic and therapeutic model. First, a blood screen aids in determining which patients undergo PET or CSF confirmatory diagnostic procedures. If positive, refer; if negative, evaluate again in the future as needed. Second level is at the CSF and PET confirmatory diagnostics for specific pathophysiological markers (not disease presence, but pathology presence). The third level adds blood-based biomarker profiles of specific biological systems known to be altered in neurodegenerative disease that may be present in addition to the pathophysiological markers identified by PET and/or CSF. The second and third levels guide specific multi-modal interventions. As an example, a patient could be positive on blood screen and then undergo both CSF evaluation for amyloid, tau, and α -synuclein. The patient, then, also undergoes blood-biomarker profiling for inflammatory, neurotrophic, metabolic, and oxidative dysfunction. A positive finding for amyloid only would move the patient to amyloid-only therapy. A positive finding for amyloid, α -synuclein, and inflammation would move the patient to multi-modal therapy targeting amyloid, α -synuclein, and inflammation.

CSF, cerebrospinal fluid; PET, positron emission tomography.

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Conclusion

The last two decades have been characterized by substantial advances in the field of blood-based biomarker investigation in AD and other neurodegenerative diseases. Human blood (plasma/serum) is the primary source of the proteome, and advanced technologies detecting even minor protein changes are key strategies to identify blood protein biomarkers. Compared with CSF markers, a validated blood-based AD biomarker has the potential to be fast, non-invasive, and cost-effective for early detection and diagnosis purposes. Moreover, since venepuncture is a routine and safe procedure (in contrast to lumbar puncture), the investigation of blood biomarkers is fully established in the clinical environment (O'Bryant et al., 2017).

The development of biomarkers mirroring all molecular pathophysiological mechanisms in the brain of patients with AD and other neurodegenerative disorders at distinct time points in disease evolution is expected to constitute the basis for personalized, tailored (i.e. adapted to the individual), biomarker-driven targeted treatments, in accordance with the evolving precision medicine paradigm (Hampel et al., 2016, 2017, 2018a). For this reason, in order to advance the development of the precision medicine paradigm in AD, the international Alzheimer Precision Medicine Initiative (APMI) and its cohort programme (APMI-CP)—available at <https://www.apmiscienc.com/>—have been launched recently by our consortium (Hampel et al., 2019). As a result, over the next few decades, a paradigm shift can be expected in which multimodal biomarker profiling, rather than clinical phenotypes, will guide therapeutic interventions. For instance, a patient showing prominent neuroinflammatory features might be treated with a special focus on brain inflammation, whereas evidence of early tauopathy will lead to tau-directed interventions. At that point, the clinical phenotype will be irrelevant and the treatment will be solidly rooted in the underlying pathophysiological underpinnings. An analogy can be found in cancer research and clinical care where classification paradigms for malignancies are expected to witness a transition from a 'tissue of origin' to an 'underlying molecular alteration(s)' model, resulting in what are hoped to be dramatically improved therapeutic outcomes (Baldacci et al., 2018).

Moreover, implementing a screening-diagnostic workflow starting with a blood-based test in primary care has the potential to increase access to second-level diagnostic tests (for instance, amyloid PET imaging) and provide a clear path for regulatory approval. Despite continuous research, several candidate blood-based biomarkers show restrictions that might preclude their application. For this reason, it is essential to establish close collaborations between academia, industry partners, and regulatory bodies to speed up the full development and validation of a blood-based biomarker assay for clinical use.

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Clinical biomarkers in the diagnosis of dementia

Chapter: Clinical biomarkers in the diagnosis of dementia

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Introduction

This chapter focuses on the current clinical application of biomarkers in the diagnosis of dementia subtypes. Discussion of more advanced or research-orientated biomarkers is limited, and further references to these can be found in chapters covering neuroimaging (Chapter 12) and blood-based biomarkers (Chapter 6), as well as chapters on dementia subtypes (e.g. Chapters 30–34).

Over the past 25 or so years, the use of biomarkers to help detect and categorize brain diseases has firmly transitioned from the ‘bench to the bedside’, mirroring their more established and developed role in mainstream medical practice.

Biomarkers now feature in the diagnostic criteria for the common types of neurodegenerative dementia, vascular dementia (VaD), and prion diseases, augmenting diagnostic confidence and accuracy. Integrating

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this evolving 'toolkit' into everyday clinical practice is becoming ever more important.

As with any investigation, the clinician needs to evaluate how the evidence for and against the utility of a biomarker can be best applied to individual patients, ensuring their use and interpretation are timely and appropriately tailored. The preferences and expectations of patients should be explored, alongside information relating to the benefits, limitations, and risks of each test. Contextual factors that could influence the choice and interpretation of biomarkers will also need consideration, such as age, medical comorbidities, stage of disease, and the differential diagnosis under enquiry, and factors relating to the test itself such as the cost, availability, and acceptability.

This chapter focuses on the application of biomarkers to diagnostic practice in the assessment of patients with suspected dementia—the judgment to use biomarkers in this context centring on their perceived 'added value' in clarifying the diagnosis under question. This added value relates to the ability of biomarkers to both 'rule out' pathologies that may be responsible for cognitive impairment, including the so-called treatable or reversible causes, as well as profile the biological signatures of dementia subtypes to positively 'rule in' their diagnosis. The clinician will need to evaluate the relevance of information provided by biomarkers, and depending on the issue at hand, the absence of a pathologic finding can be as edifying as the presence of an abnormality. A final diagnosis of the dementia subtype will ultimately rely on the synthesis of information from the full clinical assessment, informed by the outcome of any investigations.

Sharing the results of a biomarker test often plays an important confirmatory role in the disclosure of diagnosis. Optimizing diagnostic accuracy offers patients the best information to adjust to their condition and plan ahead. It also reinforces a collaborative approach, reassuring patients that their concerns have been fully appraised.

Role of biomarkers

Broadly, biomarkers are biological characteristics that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention (Biomarkers Definitions Working Group, 2001).

In the context of the clinical diagnosis of dementia subtypes, the core biomarker toolkit currently consists of imaging techniques and the analysis of CSF, as summarized in Box 7.1 and Table 7.1. Together they provide 'windows' into the structure, function, and pathology of the brain. Consensus guidelines and diagnostic criteria increasingly reference these tests. Indeed, as new technologies emerge and evidence of their utility grows, there has been a shift in the credence given to biomarkers in

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diagnostic criteria, from being a supportive feature to the status of an indicative or core feature.

Box 7.1 Clinical biomarkers used in dementia diagnosis

Main clinical biomarkers

- Neuroimaging:
 - CT
 - MRI: T1- and T2-weighted and FLAIR; plus other sequences, depending on diagnostic question
 - SPECT perfusion HMPAO
 - SPECT dopamine DaTscans
 - FDG-PET glucose metabolism
 - PET amyloid
 - CSF
- AD profile: CSF A β_{42} /phosphorylated tau/total tau
- Rapidly progressive dementia—prion diseases and infective and inflammatory forms of encephalitis

A β_{42} , β -amyloid peptide; CSF, cerebrospinal fluid; CT, computed tomography; DaTscan, dopamine transporter scan; FDG, fluorodeoxyglucose; FLAIR, fluid-attenuated inversion recovery; HMPAO, hexamethylpropyleneamineoxime; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

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Table 7.1 Summary of biomarker findings in the main types of dementia.

Diagnosis	Structural imaging	Functional imaging	CSF	Suggested sequence of tests ¹
AD	<i>Reduced</i> volume of medial temporal lobe structures	<i>Reduced</i> activity bilaterally in temporo-parietal cortex and posterior cingulate-precuneus on SPECT-HMPAO and FDG-PET <i>Increased</i> amyloid retention on PET (though application still not established in routine practice)	<i>Reduced</i> A β ₄₂ <i>Increased</i> phosphorylated tau (p-tau) <i>Increased</i> total tau <i>Reduced</i> ratio (A β ₄₂ /A β ₄₀)	Start with structural imaging—CT or MRI ² —especially looking for MTA If diagnosis remains unclear, consider FDG-PET (or SPECT-HMPAO if unavailable; FDG-PET is more accurate, however) SPECT perfusion (HMPAO) or FDG-PET can help differentiate between AD, VaD, and FTD If diagnosis remains unclear, consider LP to measure AD CSF biomarkers—or alternatively PET if available If all tests negative, then unlikely to be AD
DLB	Supportive biomarkers ³ Relative absence of MTA	<i>Reduced</i> uptake in putamen and caudate on DaTscan	–	Consider both structural imaging and DATscans from outset

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		<i>Reduced</i> uptake on 123-iodine-MIBG myocardial scintigraphy <i>Supportive biomarkers</i>³ Generalized low uptake on SPECT/PET perfusion/metabolism scan, reduced occipital activity, and relative preservation of posterior or mid-cingulate metabolism on FDG-PET (the cingulate island sign)		CT or MRI² looking for relative preservation of MTA DATscans offer high specificity and relatively good sensitivity—particularly helpful in patients with possible DLB If negative and clinical picture consistent, then diagnosis would be in keeping with possible DLB and consider repeating scan in future If diagnosis remains unclear and DLB still possible, consider MIBG SPECT, if available
VaD ⁴	<i>Presence</i> of cortical infarcts or strategic infarcts affect thalamus <i>Increased</i> deep white matter disease—shown as hypoattenuation on CT or hyperintense on T2-weighted and FLAIR MRI Greater relevance if extensive (>25% area) and confluent	Pattern of change on SPECT-HMPAO and FDG-PET is likely to vary, depending on distribution and extent of vascular disease	–	Start with structural imaging—CT or MRI² Overall—MRI is more sensitive than CT in detecting vascular changes The main causes of vascular cognitive impairment are large vessel strokes, small vessel disease, and microhaemorrhages—different MRI sequences

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				can help detect these changes T2-weighted images show infarcts; FLAIR shows white matter changes and lacunar infarcts T2* gradient echo (or susceptibility weighted imaging) can identify microhaemorrhages or microbleeds, suggestive of cerebral amyloid angiopathy or small vessel disease Additional functional imaging can be selected, depending on differential diagnosis under review 123-iodine-MIBG myocardial scintigraphy may offer greater discrimination than DaTscan in context of vascular-PD versus DLB, given it is not affected by brain vascular changes in the striatum which can mimic the pattern of nigral loss seen as a consequence of Lewy body disease

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FTD	<i>Reduced</i> volume of frontal/ anterior temporal lobes Changes can vary, depending on subtype: • Behavioural variant of FTD: varying degrees of atrophy occurring along the frontal-temporal lobe axis, occasionally including the parietal lobes • Progressive non-fluent aphasia: usually symmetrical, left-sided perisylvian atrophy (inferior frontal and antero-superior temporal regions) • Semantic dementia: usually asymmetrical (especially anterior left temporal pole) and significant ('knife edge' appearance of gyri) Atrophy may become more bilateral as the illness progresses, but usually	<i>Reduced</i> activity of frontal/ anterior temporal lobes	–	Start with structural imaging—CT or MRI², looking for frontotemporal pattern of atrophy If diagnosis remains unclear, there is good evidence to support use of SPECT-HMPAO or preferably FDG-PET perfusion, looking for reduced activity in anterior regions of the brain

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	atrophy still left > right hemisphere			

Note: The presence of these biomarker changes (in italics) provides additional evidence in support of the diagnosis. Conversely, the absence of these changes makes the respective diagnosis much less likely, especially if this is observed across all biomarkers.

¹ This is a suggested sequence, but there are many clinical factors that could vary this approach and should be taken into account.

² Choice of CT or MRI influenced by considerations such as nature of differential diagnosis, availability, tolerability, and contraindications.

³ Supportive biomarkers: these are biomarkers consistent with DLB that help in the diagnostic evaluation, but without a clear diagnostic specificity.

⁴ VaD is not a single disorder and results from a diverse range of vascular pathologies (Wardlaw et al., 2013).

A β ₄₂, β -amyloid peptide; AD, Alzheimer's disease; CSF, cerebrospinal fluid; CT, computed tomography; DaTscan, dopamine transporter scan; DLB, dementia with Lewy bodies; FDG, fluorodeoxyglucose; FLAIR, fluid-attenuated inversion recovery; FTD, frontotemporal dementia; HMPAO, hexamethylpropyleneamineoxime; LP, lumbar puncture; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; MTA, medial temporal atrophy; PD, Parkinson's disease; PET, positron emission tomography; SPECT, single-photon emission computed tomography; VaD, vascular dementia.

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In the future, the clinical use of biomarkers is likely to extend beyond facilitating diagnostic accuracy. This may include advancing pre-symptomatic detection and screening, predicting the risk of ‘converting’ from MCI to clinical dementia, profiling the often heterogeneous pathologies in individuals experiencing cognitive decline, tailoring therapies that target these changes, and then evaluating the impact of these therapies. Indeed, should new disease-modifying therapies emerge, it is highly likely this will accelerate the clinical need to provide biomarker testing prior to treatment, and healthcare systems would need to adjust to meet this new demand (Ritchie et al., 2017).

From a research perspective, biomarkers are already providing important insights into the pathogenesis, neurobiology, pre-symptomatic and longitudinal progression of dementia subtypes, and their symptoms. They are also integral to scientific and regulatory requirements of drug development and the execution of clinical trials. These roles include refining inclusion criteria, enriching the biological homogeneity of participants in clinical trials, assisting stratification, helping to reduce the number of patients required to power a study, monitoring drug pharmacokinetics including dose optimization, serving as surrogate outcome measures to validate drug responsiveness, and monitoring patient safety and adverse events.

The emergence of biomarkers has already contributed to a paradigm shift in how the diseases that underpin dementia, such as Alzheimer’s disease (AD), are understood (Albert et al., 2011; Dubois et al., 2010). A definitive understanding of the pathogenesis of such diseases remains to be determined, but we know pathogenic changes start in advance of clinical symptoms. Biomarkers can profile and track these changes, providing insights into both the pre-symptomatic and symptomatic phases of illness. This longitudinal approach broadens the perspective to view dementia as a disease with a distinct pre-dementia stage, including pre-symptomatic, then prodromal, phases. This creates opportunities to detect and hopefully prevent and/or modify the underlying diseases as early as possible.

Biomarkers are also axiomatic to a move towards a biological definition of conditions like AD (Jack et al., 2018), and combining biomarkers and genetics could lead to new approaches to defining and classifying dementia subtypes.

Need for biomarkers in diagnostic practice

Dementia is a major cause of significant morbidity and premature death, and is associated with substantial personal, family, and societal consequences. Providing a timely, accurate diagnosis is seen as a key step in helping to explain what has occurred and what is likely to follow. It will inform approaches to post-diagnostic support and help optimize pharmacological management, both in selecting the most appropriate treatment and in avoiding medications that could cause adverse effects. It

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can also facilitate access to clinical trials and other types of research. From a public health perspective, accurately detecting the prevalence and type of dementia helps to plan services and identify areas of unmet need.

Broadly, concerns about diagnostic practice have centred on both the underdiagnosis and misdiagnosis of dementia. Biomarkers can increase the proportion of patients who are correctly diagnosed.

Their value is reinforced by evidence showing the clinical diagnosis of the main subtypes of dementia can lack accuracy, when compared to autopsy-confirmed pathology. Nelson et al. (2011) found up to 30% of individuals presenting with the typical clinical phenotype of AD, as diagnosed by experts using established clinical criteria, did not have autopsy features of AD. Beach et al. (2012) also compared the accuracy of clinical diagnosis of AD with post-mortem findings and found similar concerns regarding the tendency to underdiagnose and misdiagnose a significant proportion of patients, with a sensitivity for AD of 71–87% and a specificity of 44–71%, respectively.

The sensitivity of the clinical criteria for frontotemporal dementia (FTD) can be as low as 36%, but this can be significantly improved by using neuroimaging (Mendez et al., 2007). Concerns also exist about the diagnostic accuracy of the clinical criteria for VaD (Roman et al., 1993), and the diagnostic accuracy of dementia with Lewy bodies (DLB) has been enhanced by the use of biomarkers (McKeith et al., 2017).

Individuals presenting with young-onset dementia, extensive psychiatric comorbidities, and rapid and atypical forms of dementia will also pose complex diagnostic issues where biomarkers can help clarify the underlying diagnosis.

Biomarkers in dementia represent a step towards a more accurate clinical appraisal of patients and are now incorporated in a number of major diagnostic frameworks and guidelines (such as Hort et al., 2010; McKhann et al., 2011; O'Brien et al., 2017; National Institute for Health and Care Excellence, 2018). Ultimately, they are the only way to look inside our bodies to see what may be truly happening.

Current clinical biomarkers

As noted earlier, this chapter focuses on neuroimaging and CSF biomarkers in clinical practice.

There are additional biomarkers that are relevant to certain specific diagnoses. Chapter 6, for example, provides an in-depth review of the emerging role of plasma-based biomarkers.

There are recognized genetic abnormalities associated with dementia that are usually inherited but can occasionally occur spontaneously. Examples include cerebral autosomal dominant arteriopathy with subcortical

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infarcts and leukoencephalopathy (CADASIL) (*NOTCH3*), Huntington's disease (*HTT* gene CAG trinucleotide repeat), and genetic forms of FTD (primarily *MAPT*, *GRN*, *C9orf72* expansion) and AD (APP, PS1, PS2).

Polysomnography, via sleep clinics, can be used to confirm the presence of rapid eye movement (REM) sleep behaviour disorder with atonia, which is indicative of DLB (McKeith et al., 2017). It can also help assess other sleep disorders that are associated with cognitive dysfunction such as sleep apnoea.

There is also growing evidence that myocardial scintigraphy also has utility in the diagnosis of DLB. This is another form of single-photon emission computed tomography (SPECT) that uses a tracer called metaiodobenzylguanidine (MIBG) that measures cardiac sympathetic innervation, with reduced MIBG binding being associated with DLB (McKeith et al., 2017).

Neurophysiological biomarkers include electroencephalography (EEG). This can provide supplementary evidence in the assessment of prion diseases such as Creutzfeldt-Jakob disease (CJD). Patients with CJD can have a characteristic repetitive pattern of bilateral periodic epileptiform discharge, though CSF and imaging biomarkers are more accurate. There may also be future roles for quantitative EEG and transcranial magnetic stimulation in the clinical differentiation of dementia, but currently these techniques are largely restricted to research (e.g. Cromarty et al., 2016). There is also emerging research interest in exploring the clinical utility of skin and nerve biopsies, olfactory and retinal characteristics, and abnormalities in gait patterns (see, for example, Donadio et al., 2017; Koychev et al., 2019).

Neuroimaging

Broadly, neuroimaging divides into 'structural' and 'functional' modalities. Together they provide complementary information; choosing which modalities to employ will depend on what question needs answering. Effective dialogue between the clinician and the radiologist will ensure the optimal imaging protocol is used for the differential diagnosis under question.

Structural imaging, comprising CT and MRI, captures information about the morphological appearance of the brain. Functional imaging yields information about the brain's biological activity through various 'lenses' that can sample different physiological characteristics.

All major guidelines recommend patients with suspected dementia should undergo structural imaging at least once in the course of their illness. Additional functional imaging is usually considered when the diagnosis remains in doubt and further clarification is indicated. The interpretation of functional scans should be informed by structural imaging.

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Occasionally, if the baseline neuroimaging is unremarkable (or there is an equivocal focal findings of uncertain significance), it may be relevant to repeat the investigation (usually after at least 6–12 months), depending on clinical developments.

Structural imaging in clinical practice

CT and MRI offer different advantages and disadvantages. As a general rule, CT is adequate for 'ruling out' most intracerebral lesions such as tumours, metastases, strokes, subdural haematomas, and hydrocephalus. It is also good for detecting acute intracerebral haemorrhage, bone abnormalities, calcification, and lesions with little or no water content (e.g. meningioma). Clinically, CT has tended to be used more widely than MRI, most likely reflecting its greater availability, speed, ease of use, and lower cost.

CT has a more limited role than MRI for 'ruling in' degenerative disorders, such as AD, though the development of multi-slice CT has made three-dimensional (3D) reconstruction possible, with images no longer limited to the axial plane. Most of the evidence for the utility of structural imaging in dementia subtypes is primarily from MRI studies.

Overall MRI is safer than CT, as it does not use ionizing radiation. However, scans take longer and can be less well tolerated and there are a number of important contraindications such as pacemakers and ferromagnetic objects in the eyes.

A major strength of MRI is its versatility to visualize changes in both grey and white matter, with greater resolution and clarity than CT—head-to-head, MRI will usually provide greater information to both simultaneously help 'rule in' and 'rule out' disorders. MRI is the structural imaging of choice for atypical or rapid dementias.

MRI images are 3D data sets derived from the behaviour and density of protons in water molecules when exposed to the electromagnetic environment of the scanner. An analogy has been made of how MRI creates images from the behaviour of protons with how the structure of a city can be visualized at night by mapping the pattern of streetlights. The inherent versatility of MRI lies in the variety of sequences that can be used to generate and detect different patterns of proton-related activity, which, in turn, can convey different types of information. A difference in water content of <1% is enough to distinguish between normal and abnormal tissue.

Routinely, the main MRI sequences are T1-weighted, T2-weighted imaging and fluid-attenuated inversion recovery (FLAIR). T1-weighted MRI provides excellent morphological details to study the extent and topography of atrophy. T2-weighted and FLAIR are helpful in identifying vascular disease, and the absence of hyperintensities on these scans is a strong indicator that the person's symptoms are unlikely to be due to vascular disease. These sequences also help in detecting hippocampal

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sclerosis and inflammatory, infective, demyelinating, metabolic, toxic, or infective changes. Other sequences exist and can be more relevant, depending on the differential diagnosis under assessment. For example, diffusion-weighted imaging is useful when there is rapid cognitive decline suggestive of a prion disease.

Table 7.2 summarizes the main MRI changes in less common forms of dementia.

Table 7.2 Structural neuroimaging in other diseases associated with cognitive impairment	
Disorder	Abnormalities
Variant Creutzfeldt-Jakob disease (vCJD)	Symmetrical hyperintensity on MRI in the pulvinar (posterior) nuclei of the thalamus, relative to the anterior thalamus (pulvinar sign). Hyperintensity of the dorsomedial thalamic nuclei, caudate head, and periaqueductal grey matter may also occur
Sporadic CJD (sCJD)	High signal changes in the putamen, caudate, and/or thalamus and cortical gyri (cortical ribboning) on MRI. Diffusion-weighted imaging has a high sensitivity and specificity for sCJD (especially in detecting cortical changes compared with other MRI sequences). These changes, when coupled with the absence of gadolinium enhancement and sparing of the white matter, points strongly to a diagnosis of sCJD
Progressive supranuclear palsy (PSP)	Brainstem atrophy and non-specific mild atrophy
Corticobasal degeneration	May have bilateral (symmetrical) frontal lobe atrophy—possibly extending posteriorly
Multisystem atrophy (MSA)	Olivopontocerebellar or basal ganglia atrophy, depending on variant
Normal pressure hydrocephalus (NPH)	Marked ventricular enlargement disproportionate to atrophy, with rounding of anterior horns of lateral ventricles

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Huntington's chorea (HC)	Bilateral caudate atrophy—may also have reduced volume of other basal ganglia structures and frontal lobes
CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)	Evidence of subcortical infarcts and confluent hyperintensities on MRI, potentially extending into the temporal poles (which may be non-enhancing)
Infections/inflammation	May appear as multifocal/confluent areas of hyperintensities on MRI

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The interpretation of scans should be approached in a systematic way. Harper and colleagues (2014) recommended the following order:

- Check for any 'surgical pathologies' (such as tumours, haematomas, and arteriovenous malformations).
- Assess any signal changes (based on the premise that the appearance within a single tissue type should be relatively uniform and the presence of hyper- or hypointensity within the tissue can often reflect pathology).
- Assess any atrophy, noting its pattern and extent, including areas that appear persevered. This involves checking for general and lobar patterns of cortical atrophy, noting any asymmetry and anterior-posterior gradient, as well as any evidence of basal ganglia, brainstem, or cerebellum atrophy.

Functional imaging in clinical practice

Functional imaging provides estimates of the brain's biological activity. Clinically, this is in the form of regional cerebral blood flow via SPECT perfusion, glucose metabolism via ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET), dopamine neurotransmission via dopamine transporter scans (DaTscans), and estimates of amyloid burden via amyloid PET (though, to date, in most countries, this form of imaging has not established a clear foothold in clinical practice).

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Single-photon emission computer tomography perfusion

SPECT is widely used in medicine. Images are derived by gamma cameras capturing the activity of gamma-emitting radiopharmaceuticals that have been designed to target different diseases. In the context of brain disease, two tracers have been developed—one for studying dopamine transporter function, as discussed below, and the other being ^{99m}Tc -hexamethylpropyleneamine oxime (^{99m}Tc -HMPAO).

After HMPAO is injected, it passes through the blood-brain barrier and is taken up by neurons. Image acquisition should be within 4 hours. As blood flow is closely coupled with neuronal metabolism, the images provide an assessment of the regional cerebral blood flow. The images are converted into colour maps, allowing regional patterns of blood flow/activity to be compared. The grey matter is the most metabolically active area, so it has the highest signal.

Clinical interpretation of SPECT-HMPAO scans is based on whether activity is increased or, more commonly in the context of dementia, decreased. Importantly, the pattern of loss and perseveration should be assessed and the scans should be interpreted alongside a structural scan.

Increased signal can be associated with epileptogenic foci and can be used to guide surgical treatments of refractory epilepsy.

Dementia subtypes have differing patterns of loss. Typically, AD is associated with bilateral medial temporal hypoperfusion, often in conjunction with parietal lobe hypoperfusion. Behavioural variant FTD shows a distinct anterior-to-posterior gradient (Rascovsky et al., 2011), with the frontal lobe and anterior temporal lobe showing the greatest reduction in perfusion/activity, with relative sparing of posterior areas. In DLB, there can be hypoperfusion (and hypometabolism on FDG-PET) of the occipital and posterior parietal lobes. In VaD, changes are more varied and often patchy, reflecting the varied distribution of cerebrovascular disease.

Overall, a systematic review of SPECT-HMPAO studies indicated the technique offers the best differentiation between AD and FTD—the pooled sensitivity and specificity in distinguishing AD from FTD was close to 80%, whereas the results for distinguishing AD from VaD and AD from DLB varied between 70% and 75% (Yeo et al, 2013).

FDG-PET

FDG-PET uses technology that has been widely applied in oncology for many years. Radiolabelled FDG is used to track glucose metabolism. It has a short half-life of <2 hours, and its use is limited to specialist centres as a cyclotron is required for its manufacture.

SPECT-HMPAO and FDG-PET produce similar images in terms of the topography of changes, but FDG-PET offers greater spatial resolution.

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Head-to-head, it performs better than SPECT in the differential diagnosis of AD, reaching 90% specificity and 85% sensitivity for AD versus normal controls, compared to 70% for both indices in SPECT. However, if the clinical question relates to the differentiation of DLB and AD, then DaTscans would be the first-choice functional imaging modality.

FDG-PETs are also more sensitive at detecting changes than SPECT, and changes can be observed preclinically—one of the potential advantages of functional scans based on glucose metabolism and amyloid homeostasis is that changes can be detected before the anatomical changes of atrophy are evident on structural images.

Dopamine transporter scans (DaTscans)

DaTscans are licensed for the differential diagnosis of DLB and AD. The scans are based on measuring the activity of dopamine transporter molecules in presynaptic neurons using ^{123}I -ioflupane injection (^{123}I -FP-CIT). A reduction in signal represents dysfunction or loss of nerve terminals. DaTscans have a sensitivity of 80% and a specificity of 90% to distinguish DLB from AD. They are also abnormal in other neurodegenerative conditions—idiopathic PD, CBD, PSP, and MSA. DLB should therefore not be diagnosed solely on the basis of this or other biomarkers (McKeith et al., 2017).

A normal scan shows activity in both the putamen and the caudate nuclei, producing a comma- or crescent-shaped image. This pattern is preserved in drug-induced parkinsonism and AD. In DLB, graded abnormalities are seen. Characteristically, this starts with bilateral loss of signal in the putamen, with preservation of activity in the caudate nuclei; the tail of the ‘comma’ is lost, leaving the image of a ‘full stop’. If severe, then it can be difficult to see activity in the caudate as well or to distinguish the striatum from background activity, with an overall loss of the signal-to-noise ratio.

DaTscans have been shown to improve diagnostic confidence in patients who are likely to have DLB but who present with less clear-cut symptoms. Walker et al. (2015) showed using DaTscans considerably improved the clinician’s diagnostic confidence, particularly when the scan was abnormal. The added value of imaging was evident in patients presenting with only one core feature or only suggestive features of DLB and in individuals without signs of parkinsonism.

Positron emission tomography amyloid imaging

Amyloid PET scans have been licensed to assist in the diagnosis of AD since 2013. Its adoption into clinical practice, as noted earlier, has remained limited, constrained, in part, by funding and availability, but also by the uncertainty regarding its optimal application despite a number of consensus statements advising on this issue (Johnson et al., 2013; Royal College of Radiologists et al., 2016).

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Three fluorinated tracers have been commercially developed—florbetapir and florbetaben provide grey-scale images, and flutemetamol uses colour images. They all correlate with brain amyloid deposition, particularly with neuritic plaques, but also bind to amyloid in blood vessels. The pattern of amyloid deposition on PET does not seem to follow Braak staging of AD through the cortex.

The diagnostic indication for amyloid PET scans in clinical practice centres on improving the accuracy of diagnosing AD. Their recommended role is to provide supplementary biomarker information if AD remains a possible, yet uncertain, diagnosis after a full and comprehensive specialist clinical evaluation, including conventional imaging work-up (i.e. MRI or CT) and where there is an expectation, the results will influence management (Johnson et al., 2013; Simonsen et al., 2017).

As amyloid positivity is more common with age (e.g. present in 40% of those aged over 80 years) (Ossenkoppele et al., 2015), the test will be more robust in younger individuals. Amyloid PET imaging does not distinguish between AD and DLB (Donaghy et al., 2015), limiting its value in this diagnostic differential.

Measuring amyloid is also a key biomarker when selecting participants for amyloid-based therapy studies, and its presence can predict a higher risk of converting from MCI to AD over time (Herukka et al., 2017).

To date, the utility of amyloid PET imaging in clinical practice has been uncertain. However, emerging evidence indicates it can positively influence clinical decision-making, diagnostic confidence, and patient management (e.g. Boccardi et al., 2016; Rabinovici et al., 2019). Though head-to-head comparisons of PET and CSF biomarkers (see below) are limited and discordances can occur, they appear to offer similar diagnostic performance and correlate well with each other and post-mortem findings (Blennow and Zetterberg, 2018). However, it is important to understand they provide different types information about what is happening within the CNS (Jack et al., 2018). CSF measurements are based on the dynamic balance between the production and clearance of proteins, as reflected in their CSF concentration. Molecular imaging represents the protein load or damage that has accumulated within the brain over time and, unlike the CSF, provides topographical information. As such, low CSF β -amyloid can be considered a pathologic state that is associated with amyloid plaque formation but does not measure amyloid plaque load per se like PET imaging (Jack et al., 2018).

Cerebrospinal fluid

The CSF directly interacts with the extracellular space in the brain and this proximity offers insights into brain physiology (Molinuevo et al., 2018). The CSF protects the CNS via a number of mechanisms, including regulation of intracranial pressure, providing nutrients, and supporting metabolic homeostasis. CSF volume is about 150 mL in adults and it is

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renewed 3–5 times daily. Its main molecular constituents (80–85%) are derived from blood, with the remainder coming from the CNS (Tumani et al., 2017).

The CSF can be acquired via a lumbar puncture (LP). It is a relatively invasive, yet normally safe, procedure, but contraindications include raised intracranial pressure, with a risk of cerebral herniation, as well as thrombocytopenia or other bleeding diathesis, including ongoing anticoagulant therapy. Potential side effects include back pain and headaches, and a very small number of individuals will require a ‘blood patch’ (where a small amount of the patient’s blood is injected into the epidural space near the LP site to form a clot to prevent further loss of CSF) if the headache is severe or hospitalization, depending on the risks. Adverse events can be reduced by using atraumatic (pencil-point) LP needles (Nath et al., 2018) and generally are less prevalent with increasing age (Engelborghs et al., 2017). Standard CSF analysis comprises total protein, albumin, glucose, lactate, cell count, and depending on the differential diagnosis, bacterial, fungal, and mycobacterial stains, with culture, cytological staining, and immunoglobulin G (IgG) index and oligoclonal bands.

LP should be considered if the CNS changes could be caused by infection, inflammation, or autoimmune, demyelinating, or certain neoplastic disorders.

CSF analysis has an important role in rapidly progressive dementia. This includes prion diseases such as CJD. CSF real-time quaking-induced conversion (CSF RT-QuIC) is a highly sensitive (82–97%) and specific (99–100%) test for CJD (Lattanzio et al., 2017). Elevated protein 14-3-3, S100 β , and total-tau also occurs, but with lower diagnostic accuracy, though the profile varies by the molecular subtype of CJD.

LP is also indicated for the investigation of AD. CSF changes that are characteristic of an AD profile are reduced concentrations of β -amyloid peptide ($A\beta_{42}$) and increased concentrations of tau phosphorylated at threonine 181 (p-tau) and total tau (t-tau). These changes have high diagnostic accuracy for AD, with sensitivity and specificity reaching 85–90% (Olsson et al., 2016). This AD profile is thought to relate to the core pathology of AD. It is hypothesized that the reduction in amyloid CSF is due to its sequestration within brain tissue in plaques, supported by the correlation between low $A\beta_{42}$ CSF and positive amyloid PET scans showing increased amyloid levels. Tau protein is located in the microtubules in neuronal axons. In AD, tau becomes hyperphosphorylated (p-tau) and this disrupts the normal integrity of microtubules, impairing axoplasmic flow and ultimately leading to loss of neurons and connectivity. p-tau is relatively specific to AD and a key component of tangles. t-tau, in contrast, is seen as a ‘state marker’, reflecting the intensity of neurodegeneration or the severity of neuronal damage, and

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elevated levels are seen in other conditions such as prion diseases (Blennow and Zetterberg, 2018).

Other CSF biomarkers in AD also show good discrimination, including the ratio of $A\beta_{42}/A\beta_{40}$ and neurogranin.

There is emerging evidence that CSF biomarkers may be helpful in distinguishing AD from variants of FTD, but not DLB (Paterson et al., 2018).

Procedural, laboratory, and analytical factors can affect the result and efforts to standardize these elements to improve utility. Guidance on optimal practice for CSF collection (e.g. using polypropylene vessels) and processing has been recommended—fasting is not required, but consistency when samples are acquired is important (e.g. samples should be collected between 8 a.m. and 12 noon to avoid potential diurnal variation in CSF biomarkers) (Ahmed et al., 2014).

Integrated biomarker frameworks for diagnosis of AD

Jack et al. (2018) have also proposed a framework for integrating the different biomarkers in the diagnosis of AD. This is based on the pathologic process to which they potentially link, which is summarized as 'AT(N)':

A: abnormalities in amyloid detected by CSF $A\beta_{42}$ (or ratio $A\beta_{42}/A\beta_{40}$) and amyloid PET

T: abnormalities in tau detected by CSF phosphorylated tau and tau PET (currently only used as a research tool)

(N): neurodegeneration or neuronal injury detected by anatomic MRI, FDG PET, and CSF total tau ('N' is bracketed as the changes are not specific to AD and do not map directly to the neuropathologic findings used to diagnosis AD).

According to this framework, if abnormalities in all three AT(N) domains are detected in a patient with clinical dementia, the probability this is caused by AD is increased. Conversely, if all AT(N) domains are clearly within normal limits, then AD is unlikely.

The evolution of the various biomarkers in AD has been subjected to detailed modelling. Changes begin at least 10 years before symptoms and appear to emerge sequentially in the following order: CSF $A\beta_{42}$, amyloid PET, CSF tau, FDG-PET, and structural MRI, followed by clinical symptoms (Jack et al., 2013) (Fig. 7.1).

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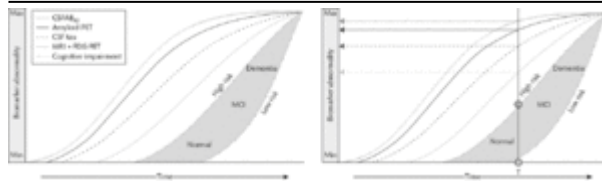


Fig. 7.1

Aβ amyloid is identified by CSF Aβ₄₂ (dotted line) or PET amyloid imaging (dark grey). Elevated CSF tau (dashed line). Neurodegeneration is measured by FDG PET and structural MRI respectively which are drawn concordantly (light grey). By definition, all curves converge at the top right-hand corner of the plot, the point of maximum abnormality. The horizontal axis of disease progression is expressed as time. Cognitive response is illustrated as a zone (grey-filled area) with low- and high-risk borders. The vertical black line denotes a given time (T). Fig. 7.1B illustrates operational use of this model. Projection of the intersection of time T with the biomarker curves to the left vertical axis (horizontal dashed arrows) gives values of each biomarker at time T, with the lead biomarker (CSF Aβ₄₂) being most abnormal at any given time in the progression of the disease. Intersection of time T with the cognitive impairment zone gives cognitive impairment at that fixed point in time. Subjects who are at high risk of cognitive impairment due to AD pathophysiology are shown with a cognitive response curve that is shifted to the left. In contrast, the cognitive response curve is shifted to the right in subjects with a protective genetic profile, high cognitive reserve and the absence of comorbid brain pathologies—illustrating that two subjects with the same biomarker profile (at time T) can have different cognitive outcomes (denoted by circles at the intersection of time T and low vs. high risk cognitive profiles).

Adapted with permission from C.R. Jack, Jr, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurology*, 12(2): 207-216. Copyright © 2013 Elsevier Ltd. All rights reserved. doi:10.1016/S1474-4422(12)70291-0.

Interpreting biomarkers

An ideal biomarker is reproducible, stable over time, and widely available and reflects directly the relevant disease process (Biomarkers Definitions Working Group, 2001). Each biomarker will, in some aspect, fall short of this ideal.

It is generally accepted that a test that performs above 80% cut-offs for sensitivity and specificity can offer clinical utility. Low levels of sensitivity can lead to too many false-negative diagnoses, delaying access to treatment, and conversely suboptimal specificity could lead to

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overdiagnosis, running the risk of inappropriate treatment and unnecessary anxiety.

It is important to emphasize that depending on the clinical question under investigation, the added value of a biomarker can lie in its negative predictive value, i.e. finding those who truly do not have the disease, as much as in its ability to show typical patterns of change.

When interpreting a biomarker such as neuroimaging, there will be a need to evaluate the overall pattern of the result, weighing up any 'abnormal' and 'normal' elements, and to do this in the context of the overall assessment.

A number of factors impact on the utility and interpretation of biomarkers. These can be grouped by the limitations of what biomarkers per se can reveal and the limitations of the validation studies used to evaluate their utility.

Limits on what biomarkers can reveal

Biomarkers may not offer a direct measure of the underlying disease process

This is relevant to a number of common biomarker changes, as described in the following examples.

Atrophy on imaging

Atrophy on structural imaging represents the visual end point of significant neuronal loss over time and therefore is seen as a proxy for neurodegeneration. It does not directly reveal the cause of this change, though the extent, pattern, and evolution of atrophy can be indicative of a particular disease. For example, hippocampal atrophy (often captured by the composite visual rating of medial temporal lobe atrophy) occurs early and progressively in AD. It is a characteristic feature of this disease, denoting the presence of neuronal damage and correlates with neuronal loss and Braak neurofibrillary tangle staging. It has a sensitivity and specificity of around 80% for distinguishing AD from normal controls, and relative preservation of medial temporal lobe structures is the most robust structural imaging findings distinguishing DLB from AD (McKeith et al., 2017).

However, it is only a proxy for this disease and it would be incorrect to infer it directly diagnoses AD. It may be absent in atypical presentations of AD (especially in young onset) and is not specific to AD. Lesser degrees of atrophy can be observed in other diseases such as VaD and FTD, depending on subtype, DLB, CBD, PSP, and Huntington's disease. A proportion of cognitively unimpaired individuals will have hippocampal atrophy, especially with advancing age, though it is usually mild. Ultimately, structural imaging can provide secondary, but not primary, evidence of diseases like AD (de Leon et al., 2007).

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White matter and vascular scan changes

VaD results from a diverse range of vascular pathologies, including large vessel to small vessel disease and micro-haemorrhages (Wardlaw et al., 2013). New imaging techniques have improved the ability to detect the spectrum of vascular changes, but their relevance will need interpreting.

Imaging can confirm the presence of vascular disease in the form of infarcts, but their clinical relevance in causing dementia still requires interpretation—strokes can occur without causing cognitive impairment and at least 20% of lacunar infarcts are clinically ‘silent’. Diagnostic criteria for VaD require a temporal relationship between when the stroke occurred and when the onset of cognitive symptoms emerged (Roman et al., 1993). This link, however, is less clear-cut in vascular cognitive impairment secondary to small vessel disease that often evolves more gradually than stroke-related dementia.

Further, the location, size, and number of strokes are likely to be relevant when inferring their impact on the cognitive and non-cognitive symptoms of dementia. Attributing cognitive impairment to vascular disease is more robust if these changes are located in cortical areas intimately associated with cognition. It is also likely ‘non-vascular’ factors are also relevant. The most consistent predictors of cognitive impairment after stroke are global atrophy and medial temporal lobe atrophy (Casolla et al., 2018). Pre-existing AD pathology may interact to increase the risk of post-stroke dementia and can potentially ‘amplify’ the impact of an infarct (Snowdon et al., 1997). Periventricular white matter changes (e.g. seen as areas of hypoattenuation around the ventricles on CT) can be due to small vessel disease, but these changes are not a direct measure of the integrity of the circulation. This change also becomes very common with advancing age, so drawing inferences about its relationship to clinical symptoms can be challenging. In addition, while white matter lesions may have an ischaemic basis in older adults, these may also be driven by Wallerian degeneration, e.g. as a result of an underlying AD process (McAleese et al., 2017).

By convention, greater clinical relevance is ascribed to white matter changes when they are more extensive (affecting >25% of white matter), confluent, and located in deep white matter—so-called ‘WMH of presumed vascular origin’ by Wardlaw et al. (2013).

Molecular biomarkers

As discussed, DaTscans measure the integrity of dopamine neurotransmission in the nigrostriatal pathways using a radiopharmaceutical that binds to the presynaptic DAT transmembrane protein. Clinico-pathological studies indicate DaTscans have a sensitivity for DLB of around 80%, inferring 20% of patients who have the pathological hallmarks of this condition at death would be inaccurately classified in life as not having this disease (if the test was used as the sole

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determinate of the diagnosis). DLB is thought to result from abnormalities in the protein synuclein, which, in turn, causes dopaminergic cell loss and the changes in dopamine neurotransmission seen in the striatum. DaTscans therefore provide an indirect measure of this pathology. Potential explanations for false-negative scans include minimal synucleinopathy affecting this area of the brain with limited nigral neuronal loss or a balanced loss of dopamine across the whole striatum (McKeith et al., 2017).

The characteristic CSF and PET changes in amyloid and tau associated with AD do not confirm the presence of AD per se. It is more accurate to think in terms of probabilities and to consider whether the biomarker findings, in the context of the overall clinical picture, make AD more or less likely. Amyloid changes can also occur in other diseases and amyloid positivity is more common with advancing age (Ossenkoppele et al., 2015).

Clinical diagnostic categories are unlikely to be pathologically pure

Approaches to the classification of dementia are on the basis of clinical features, pathological motifs, and genetics. As argued by O'Brien and Herholz (2015), we should expect this classification to change, in line with new advances in knowledge and technologies, while accepting the concordance between these elements is likely to be incomplete in the interim.

One example of this is advancing age where individuals are likely to experience a range of brain changes. Individuals with dementia are also unlikely to have 'pure' pathologies. This can make the interpretation of biomarkers more complex (as a measure of single disease). Individuals affected by AD will have amyloid and tau changes, but a proportion will also have evidence of microvascular changes, activated microglia, and other protein abnormalities such as α -synuclein and TDP-43. This overlap in pathologies with age and between different dementias means there are additional explanations for biomarker changes. This pathological heterogeneity also means it may be hard to diagnose an individual patient by measuring only a single biomarker, as often multiple pathologies are the norm.

Limitations of biomarker studies

Subjects and diagnostic groups

The reliability and validity of biomarkers are often examined using highly selected subjects in research studies, which are less typical or representative of the patients seen in clinical practice.

It is also important to evaluate which diagnostic groups have been compared in validation studies. For example, a test validated on the comparison between subjects with AD and cognitively normal individuals

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does not directly provide information about its performance to distinguish individuals with AD from a different type of dementia. This is relevant as diagnostic difficulties in clinical practice often arise in the context of differentiating dementia subtypes, rather than distinguishing dementia from normality.

Diagnostic confirmation

The utility of biomarkers is often examined by comparing their correlation with clinical phenotypes and/or other biomarkers. Their confirmatory relationship with the autopsy neuropathological 'gold standard' diagnosis is, for a series of practical reasons, often challenging to achieve. In the absence of direct clinico-pathological correlations, there will be a degree of uncertainty regarding inferences drawn from biomarker tests applied during life. An added complexity to determining the utility of a biomarker is the latency between the time when it is collected (often in early-stage illness), compared with autopsy findings (often based on end-stage illness).

Standardization of measurements and thresholds used to define abnormality

If biomarkers are to successfully transition from 'bench to bedside', the tests need to be readily and reliably available, as well as cost-effective. Overcoming these issues has been challenging. For example, up until recently, there was a lack of harmonization and standardization in how CSF biomarkers should be collected and analysed. However, it is now possible to reliably measure key CSF biomarkers using fully automated assays (Blennow and Zetterberg, 2018). Variability has also existed in how neuroimaging biomarkers are acquired and measured (Frisoni et al., 2013). The move towards using standardized visual rating of scans, such as atrophy and white matter changes on structural imaging (Harper et al., 2015, 2016; Wahlund et al., 2017) and quantification of FP-CIT striatal uptake on DaTscans, can improve their utility in everyday clinical practice, though the lack of quantification of visual scales can place a ceiling on their full potential.

Using cut-offs for biomarkers offers practical appeal in clinical practice, as they have for many other tests such as defining thresholds for diabetes or hypertension. However, there are good reasons to be cautious about an over-reliance on such binary cut-offs. There is a tendency to think of biomarkers denoting individuals into positive versus negative disease status, but invariably biomarkers are continuous measures and ambiguous or indeterminate results will be obtained (McKhann et al., 2011). As outlined earlier, factors such as age and stage of disease progression imply a dimensional, rather than a dichotomized, approach and is more in accordance with the probabilistic inferences we can draw from biomarkers.

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This dimensional approach also accords with clinical practice. The interpretation of biomarker results that are clearly above or below established cut-offs is usually straightforward, especially when multiple biomarkers show a consistent picture. However, biomarker results are sometimes intermediate or inconclusive. Depending on the clinical context, it can be appropriate to keep an open mind about the significance or otherwise of this result in case it was on the cusp of a cut-off value and becomes abnormal with time.

Gaps in evidence

It should be noted there are gaps in our knowledge relating to a number of key issues. There has been relatively few studies directly comparing biomarkers, validating how they are optimally used together, or assessing their impact on outcomes such as overall patient well-being and quality of life (Frisoni et al., 2017).

Final comments

Biomarkers can optimize diagnostic practice, helping to ensure patients and their families receive the best possible advice and treatment.

Structural neuroimaging should be considered in the investigation of all patients with suspected dementia and, where possible, performed at least once during their illness. Functional imaging and, more recently, CSF biomarkers in the context of AD provide complementary information that can enhance diagnostic accuracy.

Each biomarker has strengths and limitations and they should not be interpreted in isolation or divorced from the clinical presentation—the overarching clinical evaluation of each patient will inform which biomarker/s to select and there will always be a need to interpret the relevance of the information provided by biomarkers in this context.

The evidence to support the optimal use of biomarkers in clinical practice is still actively evolving and it is very likely that new biomarkers, whether used individually or in combinations, will emerge to offer more comprehensive, detailed, and personalized insights into brain disease.

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Molecular genetics and biology of dementia

Chapter: Molecular genetics and biology of dementia

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Introduction

Worldwide the prevalence for dementia is increasing and the incidence doubles about every 5 years. It is estimated that 35.6 million people were living with dementia worldwide in 2010, with numbers expected to almost double every 20 years to 65.7 million in 2030 and 115.4 million in 2050 (Prince et al., 2013). It is known that dementia is caused by an interplay between genes and lifestyle and environmental factors (van der Flier and Scheltens, 2005). Recent advances in genetic and molecular biology in dementia have provided valuable insights into the pathogenesis of underlying dementia for not only in those with clear genetic aetiology, but also in those with no familial basis. This brings hope for future treatment strategies and therapeutic targets. In this chapter, we focus on the four most common types of dementia: Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal lobar degeneration (FTLD), and Lewy body dementia (LBD).

Alzheimer's disease

AD is the most common form of dementia characterized by rapidly progressive cognitive dysfunction and behavioural impairment, affecting nearly 46 million people around the world. Pathologically, AD is characterized by severe atrophy and neuronal loss, extracellular neuritic plaques composed mainly of aggregated amyloid- β (A β), and intracellular neurofibrillary tangles (NFTs) consisting of hyper-phosphorylated tau protein.

Molecular biology

Amyloid and APP

The major component in plaques is A β , a 38- to 43-amino acid peptide, derived by the cleavage of the amyloid precursor protein (APP) (O'Brien and Wong, 2011). Cleavage of APP primarily occurs by α -secretase, followed by γ -secretase, to produce non-amyloidogenic products. This cleavage releases a large soluble ectodomain of APP (sAPP α) and a carboxyl terminal fragment (α CTF) (Zhang et al., 2011). The γ -secretase cleavage of α CTF produces APP intracellular cytoplasmic domain (AICD) and soluble peptide P3 (Chow et al., 2010), but a percentage of APP is cleaved by β -secretase (BACE1), rather than α -secretase, to produce sAPP β and β CTF. A subsequent cleavage by γ -secretase produces an A β and AICD fragment which are transported, via exocytosis, to the extracellular space (Masters and Beyreuther, 2006; Zhang et al., 2011). The main forms of A β produced by the amyloidogenic pathway are A β 1-40 and A β 1-42, with the latter being the more neurotoxic, which tend to aggregate into oligomers, protofibrils, and fibrils (Walsh and Selkoe, 2007). Ensuing A β plaque formation leads to localized microglial activation, cytokine release, astrogliosis, and a multi-protein inflammatory response (Eikelenboom et al., 1994; McGeer and McGeer, 1995). (See Fig. 8.1 for a summary of amyloid processing.)

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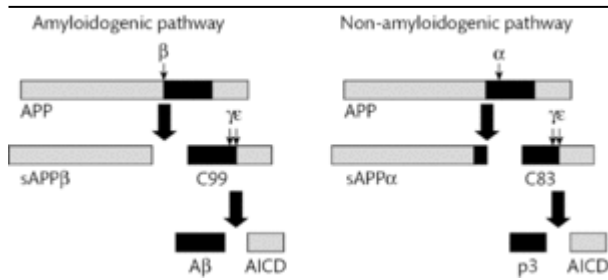


Fig. 8.1

APP processing: The APP is cleaved sequentially by enzymes termed secretases. BACE1 is an aspartyl-protease that sets the pace of A β generation. BACE1 cleaves APP in its luminal domain, generating a secreted ectodomain. The resulting 10kDa C-terminal fragments retained in the membrane, are subsequently clipped by γ -secretase, which acts at the transmembrane domain of APP to release A β . The α -secretase cleaves APP in the middle of the A β region, generating the α fragment, as well as a short C-terminal stub that is also cleaved by γ -secretase. Cleavage of α -secretase cuts APP within the A β region. Importantly, α -cleavage directly competes with β -cleavage for their common substrate APP. Subsequent cleavage of this fragment by a γ -secretase protease activity generates a secreted peptide of ~3kDa peptide (termed p3).

The 'amyloid cascade hypothesis', supported by genetics (discussed further in molecular genetics), has been the predominant model to explain AD pathogenesis. This theory suggests that APP mis-metabolism increases production, then deposition, of toxic A β and acts as a pathological trigger that leads to NFT formation, neuronal injury, and cell death (Hardy, 1992). This has been further supported by substantial genetic, biochemical, and pathological evidence (Barage and Sonawane, 2015). However, current evidence proposes that the failure or imbalance of A β clearance, rather than excess formation, is the main contributor to toxic deposition (Mawuenyega et al., 2010; Sperling et al., 2011), thus implicating mechanisms involved in the degradation of toxic A β , i.e. neprilysin, insulin-degrading enzyme (IDE), intracellular lysosomal degradation, and microglia activation, as of central importance in the development of A β pathology (Agostinho et al., 2010; Murphy and LeVine, 2010).

Tau and neurofibrillary tangles

Another hallmark in AD are NFTs, which are composed of the hyperphosphorylated microtubule-associated protein tau. A lot of neurons in the typically affected AD brain regions (entorhinal cortex, hippocampus, parahippocampal gyrus, amygdala, frontal, temporal, parietal, and occipital association cortices, and certain subcortical nuclei projecting to these regions) contain large, non-membrane bound bundles of abnormal fibres that occupy much of the perinuclear cytoplasm (Selkoe, 2001). Neurodegeneration, synaptic loss, and cognitive

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symptoms observed in AD patients are more associated with the density and distribution of NFT pathology than A β deposition (Dickson et al., 1995), although NFTs are not exclusive to AD but can occur in other neurodegenerative disorders such as Down's syndrome and frontotemporal lobe dementia.

In the adult human brain, six tau isoforms exist which are coded by a single gene located on chromosome 17 (Buée et al., 2000). By alternative mRNA splicing of exons 2, 3, and 10, six different isoforms are produced in the brain with apparent molecular weights of between 50–70 kDa (Fig. 8.2). The isoforms differ by the presence or absence of one or two short inserts in the N-terminal half (0N, 1N, and 2N, respectively) and have either three or four microtubule-binding motifs in the C-terminal half (3R- and 4R-tau) (Gong et al., 2005). In the fetal brain, only the shortest tau isoform (3R-tau) is found, whereas all isoforms are present in the adult brain. However, fetal tau is more extensively phosphorylated than adult tau (Lee et al., 2001). Prominent features of the primary structure of tau are the three or four imperfectly repeated stretches of 31 and 32 residues in the C-terminal half, which make up the core of the microtubule-interacting unit (Lee et al., 1989).

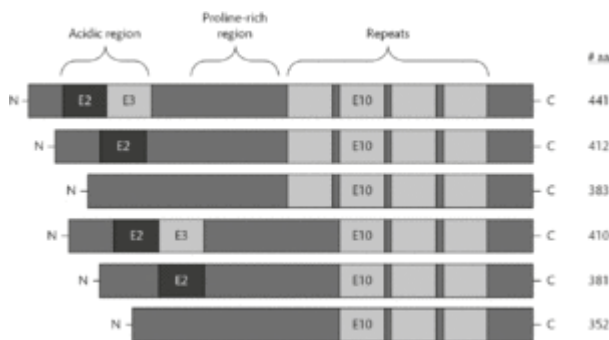


Fig. 8.2
Tau isoforms.

Hyperphosphorylated tau also forms insoluble aggregates, paired helical filaments (PHF), the primary component of NFTs found in AD and other tauopathies (Iqbal et al., 2008). Tau isolated from AD brains has a 4-fold increase in levels of phosphorylation (Kopke et al., 1993) and all tau isoforms are found to be aggregated in PHFs (Grundke-Iqbal et al., 1986). The current consensus is that A β precedes and induces a cascade that results in NFT and other pathologies (Mudher and Lovestone, 2002). Furthermore, genetic studies suggest that increased A β production demonstrates the enhanced development of tau pathology (Blurton-Jones and Laferla, 2006).

Even though the relationships between A β plaques and tau pathology remain unclear, they both finally converge to cause widespread and progressive cell death and neuronal loss. Post-mortem analysis indicates

the medial temporal lobe (MTL), including the hippocampus, parahippocampus, and entorhinal cortex, to be the first affected by AD pathology (Braak et al., 2006). As disease progresses, substantial neuronal loss in the cerebral cortex, specifically the lateral temporal and medial parietal lobes, is observed, followed by atrophy of the lateral parietal and frontal lobes (Nestor et al., 2004). During the course of the condition, an AD sufferer will have extensive atrophy of the temporal, parietal, and frontal cortices, with relative preservation of the primary occipital and primary sensorimotor cortex (Braak et al., 1993, 2011). The extent of clinic symptoms due to AD is more strongly correlated with the anatomical extent and number of NFTs in the cortex (Ingelsson et al., 2004). This observation has led to the 'tau propagation' hypothesis where tau may systemically develop and progress independently throughout the brain (Frost et al., 2009). Recent animal models strongly point towards NFT propagation from the MTL to the cortex being driven by A β (Lewis and Dickson, 2016; Pooler et al., 2015) (see Fig. 8.2).

Inflammation

Ageing is the strongest risk factor for developing AD, putatively in part as result of chronic inflammation during ageing, known as 'inflamm-ageing' (Cevenini et al., 2013), believed to be caused by both clinical and subclinical infections, as well as exposure to non-infective antigens over the course of a person's lifetime (De Martinis et al., 2005).

Neuroinflammation associated with AD is often viewed as a secondary response to A β deposition and neuronal cell death. However, there is the possibility that later neuroinflammatory response can be as pathologically relevant as an inducer. Neuroinflammation in AD is often viewed as a double-edged sword where activated microglia and reactive astrocytes, the immune cells of the brain, have both beneficial effects by degrading A β (Koistinaho et al., 2004) and adverse effects by producing cytotoxic substances that contribute to disease progression (Akiyama et al., 2000). A degree of activation is required for microglial phagocytosis of A β (Richard et al., 2008), but overstimulation ultimately may lead to neuronal cell death.

Overproduction of inflammatory molecules can affect various aspects of disease progression. Firstly, senile plaques contain many other constituents besides A β , e.g. acute phase proteins and complement factors (Akiyama et al., 2000). These A β -associated proteins have been shown to affect transport, fibrillogenesis, and deposition of A β (Eikelenboom et al., 2011; Veerhuis et al., 2005) and thereby disturb the balance between A β deposition and removal. Secondly, the cytokine interleukin-1 (IL-1) has been reported to affect A β production and deposition *in vitro*, by promoting synthesis and processing of APP (Shafteel et al., 2008).

Thus, it is becoming more evident that neuroinflammation has a substantial role in the pathogenesis of AD. It is likely that in order to

intervene in disease progression, appropriate action has to be taken against inflammation.

Synaptic dysfunction and neuronal loss

The consequence of amyloid and tau pathology is the significant loss of neurons; this loss is more pronounced in AD than normal ageing (Masliah et al., 1993). Synaptic dysfunction—ranging from altered synaptic dynamics and plasticity processes to full-blown synapse loss—is the earliest pathological feature of AD (Sheng et al., 2012). It likely begins years before functional deficits become apparent during the incipient preclinical phase of AD and is widely believed to be mediated by the accumulation of toxic A β species (Benilova et al., 2012). Since the first report of a significant correlation between synaptic loss and dementia severity (Davies et al., 1987), the effect of neurodegenerative diseases on synaptic proteins has been a subject of wide research. In AD, synapse dysfunction has been reported to occur very early in affected regions, such as the frontal or temporal cortex, and correlates more closely with cognitive decline than A β plaques or NFTs (DeKosky and Scheff, 1990; Scheff and Price, 2006; Terry et al., 1991). Levels of numerous synaptic proteins, a useful measure of synaptic integrity, are reduced in both human AD cases (Honer et al. 2003) and virtually all transgenic AD mouse models (Crews et al., 2010). However, the degree to which synaptic proteins change in AD is synapse type- and brain region-specific; distinct neurotransmitter systems also appear to be differentially affected by AD progression (Gsell et al., 2004). In this regard, cholinergic transmission seems to be affected very early, while GABAergic signalling appears to be relatively preserved, even in late AD (Davies et al., 1998). Investigating the synaptic targets affected by AD pathology, as well as the mechanisms by which this synaptotoxicity is mediated, would be highly informative and may provide novel therapeutic targets.

This is further corroborated with recent imaging biomarker studies in living patients. Even though it is very difficult to quantify the density and synaptic functioning directly in humans, FDG-PET (Herholz, 2012; Mosconi et al., 2006), functional MRI (fMRI) (Brickman et al., 2003), and EEG (De Waal et al., 2012) provide useful biomarkers for synaptic dysfunction and network connectivity in AD progression (de Wilde et al., 2011). These imaging biomarkers have, in fact, been important in helping to differentiate between disease stages and are predictive for risk of progression from normal cognitive function to MCI and AD (Sperling et al., 2013).

Molecular genetics

More recently, the advent of genome-wide genotyping has led to more genetic variants being identified as associated with AD. These genes draw attention to possible alternative pathogenesis pathways underlying AD such as lipid metabolism, the immune system, and so on. Additionally, next-generation sequencing (NGS) has continued to broaden the potential

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applications of searching for genetic contributors to AD. These NGS approaches have been applied to identify rare variants in patients with AD such as variants in triggering receptor expressed on myeloid cells 2 (TREM2), phospholipase D member 3 (PLD3), unc-5 homolog C (UNC5C), a kinase anchor protein 9 (AKAP9), and TM2 domain containing 3 (TM2D3).

AD can be divided into early-onset AD (EOAD) (<65 years) and late-onset AD (LOAD) (≥ 65 years), depending on its age of onset. Both EOAD and LOAD have a strong genetic component. Although the majority of people with AD do not present with autosomal inheritance, a few families present autosomal dominant transmission, particularly in EOAD. Meanwhile, even in LOAD, the non-Mendelian heritability is up to 80% (Gatz et al., 2006). Firstly, we will discuss the linkage studies that led to the discovery of mutations in *APP*, *PSEN1*, *PSEN2*, *a disintegrin and metalloprotease 10* (*ADAM10*), and *APOE*. Then we will summarize and evaluate the information obtained from GWAS of AD. Finally, we will outline the efforts to identify less frequent and rare variants by using NGS.

EOAD comprises the minority of all AD cases (5–10%), with an onset normally between 30 and 65 years of age. In most cases, EOAD follows a classic Mendelian inheritance pattern, usually autosomal dominant, though it can present without any family history ('sporadic' EOAD). Even though autosomal dominant AD is very rare (<1% age-specific prevalence), these discoveries of causative mutations have provided the foundation for unravelling the pathogenesis of AD and are now at the centre of current diagnosis and drug development research. Highly penetrant mutations in three genes are considered the main risk factors for EOAD: *APP* (Citron et al., 1992; Murrell et al., 1991), *PSEN1* (Tanzi et al., 1991), and *PSEN2* (Sherrington et al., 1996). These mutations have been shown to alter A β production to increase the A β 1-42 to A β 1-40 ratio, leading to dementia. *PSEN1* mutations are the most common and most severe cause of autosomal dominant AD, with full penetrance and age of onset occurring as early as 25 years of age 47. To date, almost over 200 mutations have been discovered in the three genes; for further details, readers are referred to the mutation database at <http://www.alzgene.org/> (Ferencz and Gerritsen, 2015).

LOAD is considered to be a multifactorial disease; however, there is a considerable genetic involvement. Early genetic studies in LOAD concentrated on genes involved in A β production. This led to the discovery of the best-known risk gene for LOAD, the *APOE* gene located on chromosome 19 (Pericak-Vance et al., 1991). Apolipoprotein E (ApoE) protein is the major cholesterol carrier in the brain and has key roles in neuronal growth, tissue injury repair, and immune regulation. ApoE binds to numerous cell surface receptors which are implicated in lipid delivery and transport, as well as mitochondrial function and glucose metabolism. The *APOE* gene has three allelic variations ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$) encoding different protein isoforms that differ in two sites of the amino acid sequence (Corder et al., 1993). The most common variant is APOE $\epsilon 3$

(77%), while $\epsilon 2$ (8%) and $\epsilon 4$ (15%) alleles are less common (Bagyinszky et al., 2014). On the other hand, the frequency of $\epsilon 4$ carriers in the AD population is much larger at approximately 60% (Van Cauwenberghe et al., 2016) and this equates to an approximately 4-fold greater risk for LOAD than the $\epsilon 3$ allele (Genin et al., 2011). Naturally, ApoE binds to A β peptides and effects the clearance of soluble A β and its aggregates (Bu, 2009; Castellano et al., 2011), but the APOE $\epsilon 4$ variant is less efficient in the clearance of A β (Bell et al., 2012). In addition, transgenic mouse models that express APOE $\epsilon 4$ show an inhibition of cyclophilin A signalling at the pericytes of brain blood vessels and this results in degeneration of these vessels, leakage of the blood-brain barrier (BBB) and neurodegeneration independent of A β (Bell et al., 2012). The $\epsilon 4$ allele is found to increase the risk for AD but is also implicated in the reduction in age of onset (Corder et al., 1993; Sando et al., 2008) and increases the rate of cognitive decline (Riley et al., 2000; Wilson et al., 2002). In addition, the APOE $\epsilon 4$ allele has also been found to have a stronger association with risk in women than in men (Altmann et al., 2014; Genin et al., 2011). The risk effect in heterozygous $\epsilon 4$ carriers is estimated at 3-fold, whereas a 15-fold risk is reported in homozygous $\epsilon 4$ carriers (Bu, 2009; Corder et al., 1993; Saunders and Roses, 1993). In contrast, the APOE $\epsilon 2$ allele is considered to be protective and to delay disease onset (Farrer et al., 1997; Mahley et al., 1996), although in certain populations APOE $\epsilon 2$ has been shown not to have protective effects in relation to AD (Kim et al., 1999). More recently, substantial evidence has supported a protective mechanism whereby the APOE $\epsilon 2$ allele reduces the accumulation of A β pathology in the ageing brain (Grothe et al., 2017).

Nonetheless, the presence of the APOE $\epsilon 4$ allele alone is not sufficient for the development of AD pathology (Farrer et al., 1997). In close proximity to the *APOE* gene, two possible candidates have been suggested as increased risk of AD: *TOMM40* (encoding translocase of outer mitochondrial membrane 40 homolog) (Takei et al., 2009) and *EXOC3L2* (exocyst complex component 3-like-2) (Seshadri et al., 2010). Various other candidates have been identified but have very modest association with AD. These include *ACE* (angiotensin-converting enzyme) (Kehoe et al., 1999), *ADAM10* (Kim et al., 2009), *CHRNA2* (cholinergic receptor, nicotinic, beta2) (Cook et al., 2004), *DAPK1* (death-associated protein kinase 1) (Li et al., 2006), *IL-8* (interleukin-8) (Li et al., 2009), *MTHFR* (methylenetetrahydrofolate reductase) (Chapman et al., 1998), and *SORL1* (sortilin-related receptor) (Rogaeva et al., 2007). These targets suggest that other biological mechanisms may be involved in AD pathogenesis (Ferencz et al., 2012).

More recently, efforts have been made by GWAS to identify a number of novel loci for LOAD, including polymorphisms in *SORL1*, *BIN1*, *CR1*, *CLU*, and *PICALM* (Harold et al., 2009; Hollingworth et al., 2011; Jones et al., 2010; Lambert et al., 2009; Naj et al., 2011; Seshadri et al., 2010). These discoveries have highlighted pathways related to cholesterol and lipid metabolism, energy metabolism, immune system, inflammatory

responses, endosomal vesicle cycling, and risk genes connected with A β and tau pathology. Large meta-analyses continue to be published and identify new susceptibility genes, adding further weight to implicated pathways in AD (Escott-Price et al., 2014). In a continued effort, more GWAS studies have revealed several additional susceptibility loci located in gene-dense regions: MS4A6A locus, HLA-DRB5 locus, ZCWPW1 locus, SLC24A4/RIN3 locus, NME8 locus, and CELF1 locus (Van Cauwenberghe et al., 2016); however, it is not clearly determined which genes in these regions are responsible for the association. Interestingly, a recent GWAS has identified novel genetic loci associated with hippocampal volume (Hibar et al., 2017) and novel AD loci encoding in proximity to the gene that encoded for tau (*MAPT*) (Jun et al., 2016). While none of these identified risk loci achieve the magnitude of APOE ϵ 4, they do provide vital information on the pathological pathways implicated in the disease process.

NGS studies and GWAS on very large cohorts have also revealed rare variants associated with AD. Multiple rare missense variants in TREM2 (1–2% frequency) have been reported to increase the risk for LOAD (Abduljaleel et al., 2014; Guerreiro et al., 2013b; Jonsson et al., 2013) and FTD (Guerreiro and Hardy, 2013). Individuals homozygous for TREM2 variants develop Nasu-Hakola disease characterized by early-onset cognitive problems with bone fractures and cysts. The most common disease-associated variant in TREM2 (R47H) is found within European populations and is reported to have an effect size comparable to APOE ϵ 4. TREM2 is a highly expressed receptor in microglia where it is thought to have an important role in phagocytosis (including A β) and inflammatory pathways (Guerreiro et al., 2013a; Takahashi et al., 2005).

Vascular dementia

VaD is the second most common dementia after AD, accounting for about 20% of all dementia worldwide (Gorelick et al., 2011). However, its genetic component remains poorly understood, especially when compared to other causes of dementia such as AD and FTD (Ikram et al., 2017). VaD may result from brain damage caused by numerous strokes or minor blood clots that block branches of blood vessels in the brain (Gorelick et al., 2011). Three broad subclassifications of VaD have been defined, based on underlying neuropathology: multi-infarct dementia, strategic infarct dementia, and subcortical vascular encephalopathy (Gorelick et al., 2016). A single study in 24 twins which attempted to determine the heritability of VaD was unable to identify a significant genetic component (Bergem et al., 1997). While this could suggest that the environment plays a larger role, a careful interpretation is warranted, given the limited sample size and the heterogeneity in VaD definitions (Ikram et al., 2017).

In recent years, cerebral amyloid angiopathy (CAA) has also been identified as an important risk factor for vascular cognitive impairment and dementia (Greenberg et al., 2004). CAA, a common small vessel disease (SVD), is caused by excessive A β deposition in the vasculature of

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the brain, especially in the walls of the leptomeningeal and cortical vessels (Esiri and Wilcock, 1986; Ghiso and Frangione, 2001). Besides haemorrhagic brain injury, CAA is associated with widespread ischaemic tissue injury, including white matter hyperintensities (WMHs) and microinfarcts (Reijmer et al., 2016). CAA frequently occurs as a comorbidity in AD but is also diagnosed in patients without other neurological diseases (Esiri and Wilcock, 1986; Ghiso and Frangione, 2001). In the general population, sporadic CAA occurs in elderly people (and is highly prevalent in AD brains), but rare hereditary forms are severe and have an early onset (van Opstal et al., 2017).

Single-gene disorders

A well-known monogenic disorder is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which is the most frequent heritable cause of VaD and results from mutations in the *NOTCH3* gene, mainly involving the cysteine residue, on chromosome 19q12 that cluster in exons 3 and 4 (Chabriat et al., 2009).

In hereditary cerebral haemorrhage with amyloidosis of Dutch type (HCHWA-D), an autosomal dominant form of CAA, a Glu693Gln point mutation in the *APP* gene leads to accumulation of A β in vessel walls (Maat-Schieman et al., 2005; Maat-Schieman et al., 1994). Mutation carriers develop symptoms early in life, usually between 50 and 60 years. Several variants of familial conditions related to stroke and/or dementia have been identified such as hereditary cerebral haemorrhage with amyloidosis of Icelandic type (HCHWA-I) from mutation in the *CST3* gene (Revesz et al., 2009). Inherited amyloidosis of the transthyretin (*TTR*) gene is a late-onset autosomal dominant condition characterized by deposition of TTR in the extracellular space of several organs, due to mutations in the *TTR* gene located on chromosome 18 (Vidal et al., 1996). Familial amyloidosis of Finnish type (FAF), or gelsolin-related amyloidosis occurring worldwide, is a rare autosomal dominant condition caused by G654A or G654T point mutations of the *gelsolin* gene. Chromosome 13-related CAAs include familial British dementia (FBD) (Vidal et al., 1999) and familial Danish dementia (FDD) (Vidal et al., 2000), which are novel forms of cerebral amyloidosis with extensive CAA (Frangione et al., 2001) due to mutations in the *ITM2B* (integral membrane protein 2B) gene. FBD is the current term for a rare autosomal dominant condition occurring in three British pedigrees, originally described as familial presenile dementia with spastic paralysis (Worster-Drought et al., 1933). Another monogenic form, first described in 1989, is Fabry disease (FD), an X-linked lysosomal disease due to a mutation in the *GLA* gene (Xq22), resulting in absent or reduced α -galactosidase activity that leads to accumulation of glycosphingolipid (globotriaosilceramide) in different organs (Ikram et al., 2017; Pastores and Lien, 2002).

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Other more rarely described single-gene disease entities are the COL4A1-A2 gene-related arteriopathy, which is a possible cause of small vessel arteriopathy and intracranial haemorrhages (Lanfranconi and Markus, 2010), and retinal vasculopathy with cerebral leukodystrophy, which now subsumes three previously considered separate entities (cerebroretinal vasculopathy, hereditary endotheliopathy, retinopathy, nephropathy, and stroke, and hereditary vascular retinopathy), and the disease is due to the *TREX1* gene and is associated both with SVD neuroimaging features and, in some cases, pseudotumoural lesions surrounded by vasogenic oedema (DiFrancesco et al., 2015; Richards et al., 2007). Finally, the cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), is a single-gene disorder directly affecting cerebral small blood vessels, caused by mutations in the *HTRA1* gene encoding HtrA serine peptidase/protease 1 (HTRA1), which has been described in Asians and recently in some European cases (Bianchi et al., 2014; Fukutake, 2011; Nozaki et al., 2015). Clinically, the disease is characterized by recurrent lacunar strokes associated with rapidly progressive cognitive impairment, seizures, and psychiatric disturbances (Bianchi et al., 2014; Fukutake, 2011; Nozaki et al., 2015). Although single-gene disorders are believed to account for a small proportion of cases, their prevalence is probably underestimated, and systematic studies on well-defined phenotypes and larger series are needed to help further understanding of the pathogenesis of VaD (Tan and Markus, 2015).

Candidate gene studies

Several candidate genes have been identified for sporadic VaD and most of the genes play a role in lipid metabolism [matrix metalloproteinase 1 (MMP1); matrix metalloproteinase 3 (MMP3); matrix metalloproteinase 9 (MMP9); methylenetetrahydrofolate reductase (MTHFR); paraoxonase 1 (PON1); paraoxonase 2 (PON2); very low-density lipoprotein receptor (VLDLR); sterol regulatory element binding transcription factor 2 (SREBF2), ACE I; angiotensinogen (AGT)], and inflammation [insulin-like growth factor 1 receptor (IGF1R); interleukin-1 alpha (IL-1 α); interleukin-1 beta (IL-1 β); IL6; tumour necrosis factor (TNF); transforming growth factor beta 1 (TGF β 1)] (Lee and Kim, 2013). However, most of these genetic findings have not been replicated and/or show only weak associations ($0.01 < p < 0.05$) (Ferencz and Gerritsen, 2015).

GWAS

Two GWAS have been reported to identify genetic risk factors for VaD. A retrospective study in Koreans (84 VaD patients, 200 controls) did not detect any genetic association (Kim et al., 2013), and a prospective study in the Netherlands (67 patients, 5700 controls) identified an association with the variant rs12007229 near the androgen receptor gene on the X chromosome, which was replicated in a German population (221 cases,

213 controls) (Schrijvers et al., 2012). However, large-scale hypothesis-free studies are needed for gene discovery in VaD (Ikram et al., 2017).

Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) becomes more common with increasing age and accounts for about 5% of all dementia cases in older populations (Hogan et al., 2016). The clinical and neuropathological features of DLB overlap with those of Parkinson's disease (PD) and AD (Walker et al., 2015). Due to these overlapping features, DLB is often considered as part of a spectrum, with DLB placed between PD and AD (Meeus et al., 2012).

Biology

Pathology in DLB is characterized by Lewy bodies and Lewy neurites in the brainstem, limbic system, and cortical areas (Fujishiro et al., 2008; McKeith et al., 2004). The main pathological change is the production and accumulation of abnormal α -synuclein in Lewy bodies and neurites, which is phosphorylated, nitrated, and truncated, has abnormal solubility, prompts the production of oligomeric species, aggregates into fibrils, and is ubiquitinated (Hashimoto et al., 2004; Mukaetova-Ladinska and McKeith, 2006; Spillantini et al., 1998; Tofaris and Spillantini, 2007). DLB is classified among α -synucleinopathies for these reasons with Lewy bodies or LBDs, together with PD (Goedert et al., 2001). Although genetic mutations and multiplications of the gene have been found in familial cases, the mechanism by which this protein aggregates in sporadic cases of PD, DLB, and MSA is not fully understood (Tofaris and Spillantini, 2007).

DLB has other pathologic changes such as neuron loss, microvacuolation, and AD pathology distinguished by A β deposition in the form of diffuse and senile plaques, as well as early changes of NFT pathology (Garcia-Esparcia et al., 2017). Whether the amount of α -synuclein pathology (i.e. Lewy bodies and neurites) in the cerebral cortex is predictive of dementia in LBDs is a matter of controversy (Jellinger and Attems, 2008; Parkkinen et al., 2005, 2008). Cholinergic and dopaminergic denervation of the neocortex probably accounts, at least in part, for cognitive deficits in LBDs (Garcia-Esparcia et al., 2017). Synapses are primarily damaged in the neocortex in DLB (Hashimoto and Masliah, 2003; Kramer and Schulz-Schaeffer, 2007; Mukaetova-Ladinska and McKeith, 2006; Overk and Masliah, 2014; Schulz-Schaeffer, 2010). Additional molecular alterations in the pathogenesis of DLB include impaired autophagy, the ubiquitin-proteasome system of protein (Miki et al., 2016), as well as altered responses to protein misfolding (Baek et al., 2016).

Genetics

Candidate gene studies

The first genetic studies involving DLB patients which mainly focused on families with multiple affected members with variable phenotypes, ranging from DLB to PD and AD, identified two disease-associated loci 2q35-q36 and 2p13 (Bogaerts et al., 2007; Gasser et al., 1998) and twelve disease-associated rare variants in six genes (*SNCA*, *LRRK2*, *PSEN1*, *PSEN2*, *APP*, *SNCB*) (Vergouw et al., 2017). Rare disease-associated variants have also been identified by candidate gene studies in series of unrelated DLB patients such as glucocerebrosidase (GBA) (Nalls et al., 2013; Vergouw et al., 2017).

Association studies

Exome sequencing in 111 pathologically confirmed DLB patients found that approximately 25% of cases carried a pathogenic mutation or risk variant in *APP*, *GBA*, or *PSEN1*, and the APOE ϵ 4 risk allele was significantly overrepresented in DLB patients (Geiger et al., 2016). Studies with candidate genes have shown a strong association between DLB and the APOE ϵ 4 allele (Tsuang et al., 2013; Vergouw et al., 2017). Microtubule-associated protein tau (MAPT) H1G haplotype has also been associated with an increased risk for DLB. However, the exact functional variant at the MAPT locus is still unknown, and additional studies are warranted (Labbe et al., 2016).

A GWAS has been recently reported for DLB (Guerreiro et al., 2018). In this two-stage GWAS, which included samples from 1743 patients with DLB (1324 with pathological diagnosis) and 4454 controls (1216 patients with DLB versus 3791 controls in the discovery stage; 527 versus 663 in the replication stage) from 22 centres of ten countries confirmed previously reported associations: APOE, SNCA, GBA, and a novel candidate locus CNTN1. Additionally, the authors estimated the heritable component of DLB to be about 36% (Guerreiro et al., 2018).

Other relatively new and unbiased genetic approaches, such as whole exome and genome sequencing studies, have not yet been reported (Vergouw et al., 2017).

Frontotemporal dementia

The term frontotemporal lobar degeneration (FTLD) describes a pathology of the frontal and temporal lobes, commonly associated with cerebral deposition of misfolded proteins (Lashley et al., 2015). A variable percentage of people with FTD, between 20% and 40%, present a positive family history of neurodegeneration, and approximately one-third of familial cases show an autosomal dominant pattern of inheritance of the phenotype (Rainero et al., 2017; Rohrer et al., 2009). Behaviour variant FTD (bvFTD) shows the highest percentage of positive family history at around 30–50% of patients, whereas in patients with semantic or progressive non-fluent aphasia, the frequency is much lower (Rainero et al., 2017). However, only 10–30% of pedigrees show a clear autosomal

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dominant inheritance pattern of the phenotype (Le Ber, 2013). A recent study suggested that, even in patients with late onset, FTD is a genetic-based disease with different inheritance modalities (Borroni et al., 2014b).

Biology

The neuropathology associated with FTD is highly heterogeneous. From this perspective, the FTD spectrum can be split into two major categories: FTD-tau, where pathological inclusions contain fibrillar hyperphosphorylated tau; and FTD-transactive response DNA-binding protein (TDP), characterized by neuronal and glial inclusions immunoreactive for TDP-43 (Rainero et al., 2017). In addition, there is a small group of tau-negative and TDP-negative cases that are immunoreactive to components of the ubiquitin-proteasome system (FTD-UPS) or the fused in sarcoma protein (FTD-FUS) (Josephs et al., 2011). In some cases, however, molecular classification is still uncertain (Rainero et al., 2017).

Molecular genetics

The *MAPT* gene, linked to chromosome 17, was the first mutated gene associated with FTD, and it was discovered among families who presented with FTD and parkinsonism (Hutton et al., 1998; Spillantini et al., 1998). *MAPT* mutations cause 10–20% of familial FTD and 0–3% of sporadic FTD (Benussi et al., 2015). Specifically, this gene is located on chromosome 17q21, and it consists of a non-coding exon followed by 14 coding exons (Andreadis et al., 1992). Alternate splicing of exon 10 decides the number of amino acid repetitions (3R or 4R), while alternative splicing of exons 2 and 3 establishes the number of 29 amino acid N-terminal insertions (0N, 1N, 2N), which mediate tau interactions with the plasma membrane (Brandt et al., 1995; D'Souza and Schellenberg, 2000). At present, 72 different *MAPT* gene mutations and polymorphisms have been reported, including 44 that are clearly pathogenic (<http://www.molgen.ua.ac.be>), accounting for 5–20% of familial FTD cases (Rainero et al., 2017). Depending on the type of *MAPT* gene mutation, the neuropathological phenotype varies in morphological characteristics, severity, and distribution. Mutations in exons 1 and 10 (as well as in the intron following exon 10) are associated with neuronal and glial tau deposition, while mutations in exons 9, 11, 12, and 13 lead to deposits of tau filaments, mainly in neurons (Hutton et al., 1998). Mutations in exons 12 and 13 lead to the formation of NFTs with paired helical and straight filaments (indistinguishable from those seen in AD) (Ghetti et al., 2015). Although the clinical phenotype is highly variable, earlier age of onset, parkinsonism, and oculomotor deficits should lead the clinician to suspect *MAPT* mutation in the patient; however, the lack of a clear correlation between *MAPT* gene mutations and clinical features indicates that additional genetic and/or environmental factors can produce significant phenotypic variations (Rainero et al., 2017).

Non-MAPT FTD

The progranulin (*GRN*) gene, a protein-coding gene with 13 exons located on chromosome 17p21, was found to be responsible for another 5–20% of familial FTD cases and 1–5% of sporadic ones (Baker et al., 2006; Cruts et al., 2006). *GRN* encodes progranulin, a ubiquitously expressed growth factor precursor, which, together with its products, is implicated in a wide range of biological processes such as inflammation and wound repair, as well as in pathological conditions, including tumourigenesis (Ahmed et al., 2007; He and Bateman, 2003). Progranulin is predominantly expressed at the level of activated microglial cells and this finding seems to point to its regulatory role in the inflammatory response in the brain (Rademakers et al., 2008; Philips et al., 2010). Homozygous carriers of the T-allele of rs5848 have a 3-fold increased risk of developing FTD-TDP, compared with homozygous C-allele carriers (Rademakers et al., 2008). Worldwide, 149 different *GRN* gene mutations have been described (<http://www.molgen.ua.ac.be>). Of these, 67 are clearly pathogenic (Rainero et al., 2017). Recent studies have shown in FTD patients carrying the *GRN* gene mutation that the ubiquitinated neuronal inclusions contain, as a major component, TDP-43 (Rainero et al., 2017). A loss of function of progranulin leads to defective ubiquitination, resulting in accumulation of TDP-43. Mutation penetrance is very high, with 90% of carriers manifesting symptoms by the age of 75, and the associated phenotypes are remarkably variable, both between families with different *GRN* mutations and among members of a single family (Rainero et al., 2017).

Hexanucleotide expansion repeats in the open reading frame of chromosome 9 (C9orf72)

A strong association between FTD and ALS has been known for many years. A locus for frontotemporal dementia-amyotrophic lateral sclerosis (FTD-ALS) was found on chromosome 9q21 in 2006, and in 2011, a repeat intronic expansion (GGGGCC) was identified in the *C9orf72* gene (Benussi et al., 2015; DeJesus-Hernandez et al., 2011; Renton et al., 2011). In healthy individuals, there are 2–24 non-coding hexanucleotide GGGGCC repeats, and expansion to hundreds to thousands of repeats occurs in some FTD and ALS (Benussi et al., 2015; Seelaar et al., 2011). Haploinsufficiency through the loss of gene expansion, gain of function with secondary RNA toxicity, or both, are the proposed pathogenic mechanisms (Benussi et al., 2015). The neuropathology associated with the *C9orf72* mutation is a combination of FTLD-TDP and ALS (Hsiung et al., 2012). Clinically, the predominant phenotype in these patients is bvFTD associated with ALS, although the presentation may vary widely, even within the same family (bvFTD or ALS or a combination of both diseases) (Murray et al., 2011; Van Langenhove et al., 2013).

Other rare FTD Mendelian genes associated with FTD

Mutations in the TAR DNA-binding protein 43 encoding gene (*TARDBP*) have been linked to both ALS and FTD-TDP, suggesting that TDP-43 dysfunction is mechanistic in causing disease; however, while 5% of familial ALS patients have a *TARDBP* mutation, these are rarely found in FTD or in FTD associated with motor neuron disease (FTD-MND) (Sreedharan et al., 2008; Tripathi et al., 2014). TDP-43 is an RNA-binding protein that forms heterogeneous nuclear ribonucleoprotein (hnRNP) complexes encoded by *TARDBP* on chromosome 1. The current list of *TARDBP* gene mutations includes over 40 different missenses, most of them residing in the C-terminal glycine-rich domain, encoded by exon 6 and involved in protein-protein interactions (Rainero et al., 2017). Although, in the literature, *TARDBP* mutations have been appreciated as a cause of ALS phenotypes more than pure FTD ones, they can give rise to the full FTD-ALS continuum, even to early-onset pure FTD, with no evidence of ALS, even in advanced FTD disease stages (Rainero et al., 2017).

The 'fused in sarcoma' (*FUS*) gene is located on chromosome 16q11.22 and is also a member of the hnRNP family (Sieben et al., 2012). Mutations in *FUS* are seen in ALS (50 mutations reported to date) (Sieben et al., 2012). Only four mutations have been described in FTD-MND patients, with an additional two cases with pure FTD with no overlap with MND (Benussi et al., 2015; Umeda et al., 2013).

The valosin-containing protein (VCP) is involved in protein degradation, membrane fusion, transcriptional activation, and apoptosis (Seelaar et al., 2011). In 2004, mutations in VCP were described in patients with inclusion body myopathy, Paget's disease of bone (PDB), and FTD. This was named FTDP43 inclusion body myopathy (Benussi et al., 2015). Mean age of onset ranged from 40 to 60 years (Seelaar et al., 2011). Musculoskeletal symptoms mimicking scapulohumeral dystrophy or limb girdle dystrophy were observed in 80% of patients, features of PDB in 45%, and FTD in 38% (Seelaar et al., 2011). FTD usually develop later on in the disease, classically as a behavioural variant, and early language involvement is rare. There are 19 known pathogenic mutations, with a frequency of 1.6%, and family history is positive in 80% (Benussi et al., 2015).

Pathological mutations of the chromatin-modifying 2B (*CHMP2B*) gene, located on chromosome 3p11.2, was first described in 2005 in a Danish family with autosomal dominant FTD, with a mean age at onset of 55 (range 46–65) years, and was called FTD-3 (Irwin et al., 2015). The most common presentation is the behavioural variant of FTD. Clinical features include a frontal lobe syndrome, cognitive impairment with parkinsonism, dystonia, and pyramidal signs, followed later by myoclonus (Seelaar et al., 2011; Sieben et al., 2012).

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Spinocerebellar ataxia type 17 (SCA-17) or Huntington's disease-like-4 is a rare autosomal dominant disorder caused by the expansion of the CAG/CAA repeat (coding glutamine) in the TATA box-binding protein (*TBP*) gene (Bruni et al., 2004; Lasek et al., 2006). Ataxia is common, followed by dementia (Bruni et al., 2004; Koutsis et al., 2014). The presence of neuropsychiatric symptoms, including frontal dysfunction (personality change, emotional lability, apathy, irritability, disinhibited behaviours) at the outset of the disease may mimic FTD (Bruni et al., 2004; O'Keeffe et al., 2007). Onset is variable and ranges from 3 to 75 years. Affected patients have >47 repeats and develop neurologic or psychiatric symptoms (Bruni et al., 2004; Koutsis et al., 2014; O'Keeffe et al., 2007). Reduced penetrance is reported at 44–46 repeats. Other symptoms include parkinsonism, chorea (Huntington's disease-like), dystonia, and pyramidal signs (Bruni et al., 2004; Koutsis et al., 2014; Stevanin and Brice, 2008).

Mutations in the sequestosome 1 (*SQSTM1*) gene were initially identified as a cause of PDB, a common disorder of bone metabolism characterized by increased tissue turnover. However, mutations in *SQSTM1* have been found in both sporadic and familial ALS patients (Fecto et al., 2011) and also in FTLN patients (Rubino et al., 2012). *SQSTM1* is an 11-exon gene located on 5q35 and it encodes p62, a 440-amino acid adapter protein containing several proteins. However, at present, no clear genotype-phenotype correlations have been demonstrated (Rainero et al., 2017).

Homozygous deletions of exon 5 of the gene encoding optineurin (*OPTN*) have been described in Japanese siblings affected by ALS (Maruyama et al., 2010). The heterozygous triggering receptor expressed on myeloid cells 2 gene (*TREM2*) is a 5-exon encoding gene on 6p21.1, and *TREM2* mutations modulate the risk of FTD, in addition to increasing susceptibility to AD (Borroni et al., 2014a). A study identified different homozygous mutations in *TREM2* in three Turkish probands among 44 identified with FTD spectrum-like disease (Guerreiro et al., 2013a). Fourteen different mutations have been identified since in *TREM2* and an increased frequency of rare heterozygous *TREM2* variations were also detected in AD patients (Jonsson et al., 2013). Two new genes have been reported to be mutated in patients with FTD: *CHCHD10* (coiled-coil helix-coiled-coil-helix domain containing 10), which is located on chromosome 22 and encodes a mitochondrial protein that is enriched at cristae junctions in the intermembrane space; and *TBK1* (TANK1-binding kinase 1), which is located on chromosome 12 and encodes a serine/threonine kinase that plays an essential role in regulating inflammatory responses to foreign agents (Freischmidt et al., 2015; Zhang et al., 2015).

GWAS

In the first GWAS on FTD patients, a group of 515 individuals affected by FTLN with autopsy-proven TDP-43 inclusion pathology (FTN-TDP) were compared with 2509 healthy controls and an association with three single-nucleotide polymorphisms (SNPs) mapping to a single linkage

disequilibrium block on 7p21 was shown (Van Deerlin et al., 2010). Later, a two-stage GWAS was performed in a large cohort of 3526 FTD patients, in comparison with 9402 healthy controls, and a significant association at 6p21.3, HLA locus, together with a potential novel locus at 11q14, encompassing RAB38/CTSC (the transcripts of which are related to the lysosomal pathway), were found for bvFTD (Ferrari et al., 2014), suggesting that immune system processes, and possibly lysosomal and autophagy pathways, are potentially involved (Ferrari et al., 2014). A novel genetic insight into FTD and its clinical subtypes using a joint-SNP gene-based approach in 3348 clinically identified FTD cases and 9390 controls identified an association of the *TOMM40* and *APOE* genes with bvFTD, and the *ARHGAP35* and *SERPINA1* genes with progressive non-fluent aphasia (Mishra et al., 2017). The APOE-locus association with bvFTD indicates its potential risk-increasing role across different neurodegenerative diseases, whereas the novel genetic associations of *ARHGAP35* and *SERPINA1* with progressive non-fluent aphasia point towards a potential role of the stress signalling pathway in its pathophysiology (Mishra et al., 2017).

Conclusion

Molecular genetics of neurodegenerative disorders has come a long way, with the advent of large-scale GWAS and the most recent NGS. This has given us some great insight into the possible underlying mechanisms involved in these diseases. Interestingly, there is a common theme among the neurodegenerative diseases, and these genetic studies have outlined several pathways such as immune response, lipid metabolism, protein folding, and protein transport. This has led to several innovative approaches to targeting novel drug therapies, and many others will be discovered. Finally, most dementias are multifactorial and are not caused by genetic factors only. Therefore, more research is needed, particularly investigations of epistasis and gene-by-environment interaction.

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Psychiatric assessment of older people

Chapter: Psychiatric assessment of older people

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Aims of the psychiatric assessment

The psychiatric assessment of the older person aims to provide an understanding of the symptoms the person is experiencing, so that diagnoses can be made and appropriate management plans formed. It is also a crucial opportunity to engage the person and commence a therapeutic relationship. A thorough assessment of all the potential needs of an individual is likely to take more than one assessment. The initial assessment should aim to gain an overall understanding and prioritize which areas should be the focus of any immediate management plans and any other areas that may need further subsequent assessment. In many ways, the structure of an initial psychiatric assessment is the same as in younger people, consisting of a thorough history taking, a detailed mental state examination, and a physical examination. However, both the balance of areas examined and the specific questions used should be adapted for older adults.

Psychiatric assessment of older people

Context of assessment

The immediate context of the assessment is the starting point and provides important information. Clinicians need to be flexible, to ensure the initial assessment is conducted in the most appropriate context, whether in the patient's home, an outpatient clinic, or residential care or on an inpatient ward. There are significant benefits to initially assessing patients at home, for both the patient and the clinician. Assessing someone at home allows them to be at their best in their environment, giving a more realistic assessment of mood, cognition, and general behaviour, and allows a more thorough assessment of their context, including family dynamics and their home environment, than would be possible in the clinic. Observing the general level of cleanliness, evidence of trip hazards such as loose carpets or objects on the floor, and, after permission, a quick inspection of the fridge and kitchen can provide important information into environmental risks and the level of function (Ng and Atkins, 2012). Note should be made of the level of clutter or hoarding, trip hazards, and fire safety, including the presence of smoke alarms. There may also be written care plans available from carers or district nurses and it is useful to ask the patient to show the clinician their medication, both to confirm doses and to look for evidence of compliance. These benefits of home assessments are complemented by evidence suggesting that patients (Jones, 1987) and general practitioners (Hardy-Thompson et al., 1992) prefer home assessments to outpatient appointments. In addition, home visits are more flexible than, and as time-efficient as, outpatient clinic assessments (Benbow, 1990) and are associated with less non-attendance (Anderson and Aquilina, 2002) and more effective follow-up.

There is clearly a wide range of other contexts in which older people are assessed, including inpatient units, acute hospital settings, police stations, general practice surgeries, care homes, and day services. A significant number of referrals to old age psychiatric services come from wards in general hospitals, and assessment of patients by old age liaison services requires further specialist skills and approach, which will be discussed in Chapter 24. Another common setting for conducting an assessment is in a care home. In this context, it is important to gather initial information from social services, records of previous medical assessments that may have been made prior to moving into the care home, and any available care records from care staff. This will help to ascertain the reason the patient is living in a care home and enable the focus of the assessment to be on current issues. If the assessment takes place in the outpatient setting, simple factors such as whether the individual was able to arrive on time, if they drove or came on public transport, and who is with them can provide useful information about function.

Along with the geographical location of the assessment, the time frame is also important. Is the assessment urgent or routine? How has the person accessed the service? Who referred them and why? This information

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should be available from the referral documents prior to meeting the person and provides important context before a face-to-face meeting. In addition, there are several patient factors that need to be considered in advance, if possible. Is a translator required, or are there any cultural sensitivities around the timing or location of the assessment that should be considered? Are there any potential risks to the clinician in conducting the assessment, particularly with home visits? Is there any information from the referrer about important sensory or communication difficulties that may require additional resources (e.g. use of Braille or picture boards)? If the referral has been made by primary health services or social services, it is important to access as much information as possible about the person in advance of the assessment.

The psychiatric assessment

At the start of the assessment, it is important to clearly introduce yourself, explaining who you are and why you are there. It is not uncommon for individuals to not be aware that they have been referred, as this may have been precipitated by concerned relatives. Tact and sensitivity are needed to explain the concerns others may have about the patient and also to explain the reason for, and the purpose of, the assessment. If a person refuses to be assessed, then it may be necessary to consider the potential urgency and risk and whether an assessment will need to be arranged subsequently under the Mental Health Act. In these circumstances, clear communication with the referrer and other relevant agencies, such as social services, is vital.

A collateral history from a relative or friend is almost always useful and should form part of the assessment, particularly in people with cognitive impairment. It is therefore important to ask permission to speak to a relative or friend, although this should be done sensitively. It is usually better to speak separately to a relative or friend to gain collateral history, and then to speak individually to the patient. However, often the patient will request to have a friend or a relative present throughout the assessment, and this can also provide a useful insight into their communication, awareness of potential behaviour or symptoms, and relationship dynamics. During the general introduction, it is also clearly important to clarify whether the patient has any visual or hearing aids they require and is comfortable and able to engage in an assessment as best they can. Table 9.1 summarizes the general approach set out in this chapter.

Table 9.1 General approach to history and examination.

History	Mental state examination
History of presenting complaint	Appearance and behaviour

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Past psychiatric history	Speech
Past medical history	Mood
Medication and allergies	Thought
Drug and alcohol history	Perception
Family history	Cognition
Personal history	Capacity
Premorbid personality	Risk
Social history	
Forensic history	Physical examination

History

As with all psychiatric assessments, the history is the main focus. For individuals referred to a service, the presenting complaint may be stated by the referrer. However, it is useful to ascertain why the individual thinks they are being assessed and how aware they are of the assessment. In people with cognitive impairment, it is not uncommon for them to be unaware of any difficulties and therefore to deny any 'presenting complaints', and a simple opening question such as 'how can I help you' or 'what brings you to clinic' may be met with a denial of any difficulties and an expression of surprise or anger at the referral. A more open question such as 'is there anything that has been concerning you?' or 'do you have any concerns about your memory?' may be a useful starting point, or engagement in a neutral topic of conversation to begin with to build rapport.

History of presenting complaint

The major focus of an assessment is to identify what the main problems are, what has led up to the current presentation, and why the person is seeking help or been referred now. The duration, pattern of onset, and time frame of the presenting problems are important and may help differentiate acute versus chronic confusional states and identify any clear precipitating factors. Decisions as to which open and more closed questions to ask will be framed by the context and most obvious presenting symptoms. For example, a memory assessment will precipitate questions relating to duration, pattern of onset, and progression of memory difficulties. In contrast, a report of low mood will precipitate questions regarding the onset and duration of depressive symptoms,

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including sleep disturbance, fatigue, or loss of interest in living and previously enjoyed activities, which may be more prevalent in late life depression than in younger adults (Fiske et al., 2009). When assessing the duration of illness or evidence of change with time, it can be helpful to ask how they were at a point in the recent past, e.g. last Christmas, and how things have changed since then. If there is concern regarding cognitive impairment, it is also important to cover the range of non-cognitive symptoms that occur in dementia, including social interaction, mood, paranoia, hallucinations, agitation, sleep, and wandering. Questions should also be asked about difficulties with everyday function, recording specific examples and noting areas that may require further specialist assessment by occupational therapy or social services. A collateral history will be very useful here, as having the opinion of an informant regarding what the main issues are and how they have developed and presented may help to build a more complete picture of recent events and the main problems that may need addressing.

Past psychiatric and medical history

It is important to establish as clear a history as possible of previous or concurrent psychiatric and medical illnesses. Medical comorbidity is common in patients referred to old age psychiatric services (Loi and Chiu, 2011), and therefore, it is the norm, rather than the exception, to have multiple physical conditions that may impact on mental health, and vice versa. An account of whether the person has had any previous diagnoses of psychiatric illness, including how that was managed (e.g. inpatient versus outpatient, pharmacological versus psychological therapy), and the context is useful, given the relapsing-remitting nature of many psychiatric conditions. A history of the severity of any previous episodes of psychiatric illness is important, including history of self-harm or aggression, use of the Mental Health Act, and length of episodes. If possible, a history of which treatments have proved beneficial in the past or whether any medications have been unsuccessful or led to side effects is important. Establishing what factors have been helpful or unhelpful in managing previous episodes and how the person wants to receive support can aid recovery. As with all areas of the history, a collateral history from an informant or from the general practitioner (GP) is often necessary, as patients may forget or brush over previous illnesses. It is useful to confirm any medical conditions recorded on GP referral records, both to establish the past medical history and as a way of assessing whether the patient has impaired recall of major events or illnesses.

Physical health conditions can have an enormous impact on mental health and as full a history as possible of previous and current physical conditions is important. Specific attention should be paid to common 'vascular risk factors' that increase the risk of dementia such as diabetes, hypertension, hypercholesterolaemia, stroke, and myocardial infarction (Gorelick, 2004). A sense of the patient's understanding or anxiety relating to their physical health is also important, as this may help assess the precipitant for the current presentation. It is also helpful to try and

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establish who else is currently involved in the person's care, to enable clear communication between specialties and prevent unnecessary investigations or conflicting management strategies. Any recent hospital admissions and ongoing outpatient care should be noted, including any forthcoming procedures or investigations.

Medication

Polypharmacy is very common and many medications may have side effects that impact on mental health. For example, the impact of anticholinergic side effects of common medications on cognition may be missed or underestimated (Bishara et al., 2017). Any recent additions or changes to medication should be noted, particularly if the patient has recently had an admission to a general hospital.

Treatment adherence should also be assessed, and a benefit of home assessments is the ability to ask patients to show you their medication. This helps to assess both their awareness of what medication they are meant to be taking and why, and enables a more accurate record of what medication is actually taken. Tablet blister packs, dosette boxes, and dates can be checked to identify if there is any evidence of accidental or deliberate non-compliance. It also aids an assessment of the risk of accidental or deliberate overdose by demonstrating what medication is in the house and how it is accessed.

Any known drug side effects or allergies should be recorded, along with any other relevant observations or reports such as difficulties with swallowing medication, opening blister packs, or administering insulin.

Drug and alcohol history

Alcohol use in older people is common (O'Connell et al., 2003) and abuse of other substances may also be an issue (Kuerbis et al., 2014). Previous and current alcohol and illicit drug use should therefore be assessed, as should potential dependence on analgesics (particularly opiates) or benzodiazepines. Alcohol intake should be assessed in terms of daily or weekly units and any evidence of hazardous drinking and impact on physical health and psychiatric symptoms.

Family history

A brief family history of psychiatric or medical illnesses is useful, although it may be difficult to corroborate this information. This allows assessment of illnesses that may have some increased risk in first-degree relatives, but also experience of illness in the family (e.g. experience of a parent or sibling with depression or dementia) that may impact on the person's awareness or concern about their own symptoms. It also allows an assessment of the family tree, including whether there are any living relatives. Asking about family history is also an opportunity to assess

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recall of autobiographical information as part of the assessment of cognitive function.

Personal history

A personal history sets the context of the individual and is important for understanding the patient as a person. It enables an insight into important events in their life that shaped them and may have continued impact or relevance. In many cases, particularly in individuals with cognitive impairment, it also enables a way of assessing autobiographical memory that may seem less confrontational than more formal cognitive assessment. It can also be a useful line of questioning to build rapport and demonstrate interest in the individual. For this reason, it may often be helpful to move to the personal history near the beginning of the interview, because patients may happily talk about their early life, as important dates or anecdotes from early life may be more easily remembered than more recent events.

Relevant areas include any significant difficulties around birth and early development, and a brief understanding of their childhood context can be helpful in identifying current relational dynamics.

An overview of schooling and academic ability, such as school-leaving age, examinations passed, and any higher education or vocational qualifications, can be helpful, particularly when assessing cognitive function and evidence of decline. However, often patients may have left school at age 14 or have limited education due to socio-economic or cultural reasons, so care should be taken not to infer the level of intelligence from education. A brief overview of their employment history is also useful, including reasons they stopped work, any concerns about current employment, and the range of employment, as these provide important insight into their life and the potential impact of any medical or psychiatric illness.

Family and personal relationships are also key in understanding a person's history and current circumstances, both in terms of support and areas of conflict or distress. Information about their relationship with parents and any siblings, including ongoing relationships, is useful. A history of relationships, including marriage and current partner, any children, and grandchildren and their level of contact and involvement, is important, as an assessment of the social network and level of support available from friends and family is a crucial part of both assessment and considering management options.

Premorbid personality

Establishing a sense of a patient's premorbid personality may help to provide evidence of recent change. It can be useful to establish if they are predisposed to anxiety, depression, grandiosity, or aggression and to identify personality changes that may accompany dementia, particularly

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FTD. Asking how a patient sees themselves now and asking an informant how they have changed can be helpful in this respect.

Social history

The social history provides an opportunity to gather information about a patient's current social setting, the level of support or care needs, and everyday function. Information on the type of accommodation (e.g. flat, house, bungalow) and whether it is privately owned or rented and what agencies (e.g. social services, housing association) are involved is useful. It is also important to ask about access—do they have stairs and, if so, are they able to manage them? Do they live in a block of flats, and is there a working lift? How often do they leave their accommodation? It is also helpful to ask about the setting—do they feel their neighbourhood is dangerous, safe, isolated, or noisy? The quality of relationship with neighbours can be key both for support and potentially in the development of symptoms (e.g. persecutory delusions or partition delusions in late-onset psychosis).

It is helpful to ask about the patient's current range of social activities and hobbies. What do they enjoy doing and who do they see on a regular basis? Are they a member of any clubs or societies? Asking if they are able to do activities they used to enjoy may give clues towards cognitive or functional change or depressive symptoms. Do they have any ongoing responsibilities or childcare, e.g. looking after grandchildren?

Any areas of function not already addressed in the history should be explored here. Is the patient able to manage ADLs such as washing, cooking, cleaning, using the telephone or Internet, and shopping? Do they have professional carers, and, if so, are these privately funded or coordinated by social services? What services do carers provide and how often? Do they feel this is enough, or too much? Do they continue to drive or are they able to use public transport? Have they had any incidents or near misses when driving or got disorientated and lost when out of the house? Asking an informant about driving safety can be important and it may be necessary to ask the patient to stop driving in order to allow further assessment to take place. Clinicians should be aware of Driver and Vehicle Licensing Agency (DVLA) guidelines on driving for patients, including the requirement for all people with a diagnosis of dementia to inform the DVLA and to adhere to these. Driving is discussed in more detail in Chapter 57.

Finances should also be enquired about. How do they manage their finances, pay bills, or access any pensions or benefits? Is there a lasting power of attorney in place? Do they have any concerns about finances? The possible risk of financial exploitation and abuse of older people needs to be considered and safeguarding concerns raised with social services if this is suspected (Crosby et al., 2008). Although this may not be a discussion for an initial assessment, it may also be important to establish

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if the patient has any wishes for future care, and this may lead to important discussions around advance care planning.

Forensic history

It is important to ask whether the patient has a forensic history, both as part of the autobiographical history and to inform risk assessment.

Collateral history

Finally, and as indicated several times already, a collateral history from an informant who knows the patient well is often critical in gaining a full understanding of the presenting complaint and individual. This may be from a caregiver, friend, or family member. It is important to establish how well the informant knows the person and how frequently they have contact, as this may impact on how reliable any observations of change in behaviour are. For example, observations from a family member who lives with the person will differ from a friend who only has intermittent telephone contact. Asking an informant for their account and opinion of what the main issues are can be helpful both to provide information and to establish the priorities for management. With the permission of the patient, it may be helpful to have a conversation with an informant away from the patient, as a carer or family member may be reluctant to speak openly about their concerns in front of the patient. Although it is not generally appropriate to carry out a formal assessment of this, care may be needed to pick up any evidence that the informant may themselves have cognitive impairment or a mental disorder influencing the accuracy of the information provided, as well as wider considerations of reliability such as ulterior motives or safeguarding issues. Multiple informants may be required where these complications are suspected.

Mental state examination

Appearance and behaviour

As in all areas of psychiatry, the appearance and behaviour of the individual can provide an enormous amount of diagnostic information. Personal appearance may give information about whether they are able to maintain personal and dental hygiene, shaving, and cleanliness. Are they dressed appropriately for the setting and temperature? Does it seem like their clothes fit and are washed, or are they put on incorrectly or stained? If they live alone, are they able to maintain their own washing and dressing? A benefit of conducting home visits is the ability to assess the home environment. Is the home clean and tidy or disorganized, dirty, and demonstrating potential evidence of neglect, environmental dangers, hoarding, or squalor that may require urgent intervention? Poor self-care may be present in a range of conditions, including dementia, depression, and psychotic illnesses (Pavlou and Lachs, 2008).

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Alongside observation of the physical appearance, how is the patient's demeanor and eye contact? Are they calm and cooperative with the assessment, or hostile and aggressive? Are they agitated or anxious, picking at their hands or clothing? Do they seem distracted and have difficulty attending to you or the conversation, which may indicate delirium, depression, or psychosis? Do they show the characteristic minute-by-minute fluctuation often seen in delirium? Are they able to answer questions and engage, or are they constantly looking to a family member or friend for support and reassurance, which may suggest cognitive impairment, anxiety, or depression? In older people, psychomotor changes can be especially prominent in affective disorders, with agitation a common feature of depression (Fiske et al., 2009). Apathy is common in early dementia and may be mistaken for depression (Robert et al., 2009). However, a patient with apathy may be able to engage well when directly addressed and show a reactive mood.

The presence of relevant medical comorbidity may also be evident. For example, is there a tremor or evidence of hemiparesis? Is there significant deafness or visual impairment? Are they mobile or chair- or bed-bound? Observations of this kind will also obviously depend on the setting of the assessment, as seeing a person in an acute hospital setting may create a different set of expectations around their appearance and behaviour, compared to assessing someone in an outpatient clinic or in their own home.

Finally, what is their posture and body language towards you and others? Are you able to build a rapport with the person, or are they guarded, dismissive, hostile, or irritable? Are they inappropriately tactile or flirtatious in their manner? Do they turn away or refuse to look at you, or make threatening or aggressive gestures? It is important to maintain your safety and that of the individual, and therefore, note any aggressive postures and terminate the assessment if necessary.

Speech

The assessment of speech should note the rate, rhythm, and volume. If speech is abnormally rapid, can it be interrupted and, if so, for how long? Are there any spontaneous pauses or will it continue indefinitely? However, in older adults, it is more common to experience patients with impoverished or quiet speech and dysphasia, which may occur in dementia and neurological conditions. As depression is more common than mania in older adults, a reduced rate and poverty of speech is more often seen than loud or increased rate of speech. Finally hearing impairments are common in older people, and therefore, the quality of speech or apparent understanding may be due to deafness, rather than receptive dysphasia. The assessment of dysphasia is covered in detail in Chapter 11.

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Mood

The assessment of mood follows a similar approach to that in younger adults. However, some features of depression are more prominent in older than younger adults. In addition to asking about the subjective experience of low or elevated mood, subjective complaints of poor memory and concentration are also common among depressed older adults (Fiske et al., 2009). Depressive illness in older adults may also be accompanied by more prominent psychomotor retardation or anxiety than in younger adults. Therefore, a presentation of anxiety and agitation in an older adult warrants a careful assessment for depression. In depressed older people, thoughts of wanting their life to end may be present, but active suicidal ideation is rarer and any suicidal thoughts should be taken seriously and carefully assessed (see Risk assessment, p. 150).

Objective assessment of affect needs to consider medical comorbidity. Parkinson's disease may lead to reduced facial expression, which needs to be considered when assessing affect. Cerebrovascular disease may be associated with mood lability, which may present as apparently spontaneous, but typically short-lived, episodes of weeping without any substantial lowering of mood, particularly following stroke (Calvert et al., 1998). Elevation of mood tends to be less significant in mania in older adults than in younger people and may also be seen in FTD.

It is also the case that older adults may be more reluctant than younger adults to discuss their feelings and may minimize their symptoms. Therefore, close attention needs to be paid if a patient is apparently dismissive about their mood.

Thought

Form of thought, sometimes described under 'speech', rather than 'thought', in the mental state examination, may be difficult to assess in patients with dysphasia. The presence of organic brain disease or acute confusional states may also present with apparent thought disorder, and disentangling a 'pure' functional thought disorder from cognitive impairment can be challenging. Abnormalities in the form of thought (including thought withdrawal, broadcast, and insertion) can occur in schizophrenia, depression, and bipolar illness. However, formal thought disorder is less common, and possibly even absent, in late-onset schizophrenia (Howard et al., 2000). Incoherence of thought is common in dementia and more common in advanced disease, although it can also occur in the early stages. As with pressured speech, a few minutes' observation during an appropriate point in the conversation may help to delineate the severity of formal thought disorder according to the length of time a coherent theme (or response to a question) is maintained before moving off-topic. It may also be helpful in delineating persistent thought disorder accompanying psychotic states from the more fluctuating mental state characteristic of delirium.

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Delusional ideation in older adults may take different forms, depending on the underlying condition. Within AD, paranoid and persecutory delusions are common. These have been divided into delusions of theft, harm, morbid jealousy, and abandonment (Reeves et al., 2012).

Misidentification phenomena are also common in AD and include a range of beliefs such as 'phantom boarder' (the belief that someone else is living in their home), the belief that people seen on television are really present in the room, the 'mirror sign' (where patients fail to recognize themselves in the mirror, believing themselves to be a stranger), Capgras syndrome (the belief that a relative or carer has been replaced by an imposter), and belief that 'this house is not my house' (the inability to recognize one's home environment) (Reeves et al., 2012).

Within severe depressive illness, mood-congruent nihilistic delusions may be present. In late-onset schizophrenia, persecutory delusions and partition delusions are common (Howard et al., 2000), and while complex and sophisticated delusions are unusual in dementia, these remain typical of schizophrenia in either its early- or late-onset forms. As with other aspects of the mental state, delusional beliefs may be expressed in delirium but are characteristically fluctuating and inconsistent.

Perception

Perceptual abnormalities may be auditory, visual, olfactory, gustatory, or tactile. As well as occurring in psychoses, perceptual abnormalities may be described in patients with primary visual or auditory pathology or in delirium and forms of dementia, particularly LBD and PDD. Delirium is a common cause of perceptual abnormalities, particularly visual and tactile hallucinations, and should always be considered.

Auditory hallucinations may range from simple, unstructured sounds to voices heard in the second person or third person, as a running commentary, or as thought echo. Hallucinations of unstructured sounds may occur in acute organic states. However, more complex auditory hallucinations and specifically hearing voices are most characteristically experienced in schizophrenia or affective psychoses (Oyebode, 2015).

In comparison to auditory hallucinations, visual hallucinations more characteristically occur in organic states, rather than in functional psychosis (Waters et al., 2014). Visual perceptual abnormalities may range from illusions to fully formed hallucinations (Norton and Corbett, 2000). In some cases, it may be difficult to be sure whether the visual hallucination is truly occurring in the absence of a real stimulus or whether it is a misperception resulting from poor eyesight or some other defect in visual processing. Charles Bonnet syndrome presents with complex visual hallucinations, usually in association with visual system pathology, but without significant cognitive impairment, alteration in consciousness, or demonstrable psychopathology (Ffytche and Howard,

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1999). The characteristic visual hallucinations in LBD are often complex and of people or animals (McKeith et al., 1996).

Olfactory hallucinations may occur in epilepsy, particularly temporal lobe epilepsy, schizophrenia, and other organic states (Velakoulis, 2006). Late-onset schizophrenia may be more likely than early-onset schizophrenia to present with visual, tactile, and olfactory hallucinations and third-person, running commentary, and accusatory or abusive auditory hallucinations (Howard et al., 2000).

Cognition

A detailed description of cognitive assessment is provided in Chapter 10. Cognitive assessment is obviously crucial in the assessment of the older person. In some settings, it may be appropriate to formally assess the cognitive function of an individual early in the assessment, as an understanding and interpretation of other symptoms or reliability of the description of events may depend on establishing whether there is evidence of cognitive impairment. During an initial assessment, a broad assessment tool such as the MMSE (Folstein et al., 1977) or Montreal cognitive assessment (MoCA) (Nasreddine et al., 2005) may be sufficient to provide evidence of whether cognitive impairment is present. However, a more detailed cognitive assessment is often very useful and necessary to enable the diagnosis of subtypes of dementia and give a full understanding of preserved abilities and areas of specific difficulty. In situations when cognitive assessment is refused or is not feasible, some clues as to impairment may be gathered, as mentioned, from the history and other aspects of the examination (e.g. observing for fluctuating attention, characteristic of delirium), but a reliable informant account is likely to be invaluable.

Insight and capacity

The assessment of insight is important, as willingness to engage with services and treatment plans is strongly influenced by an individual's insight into their illness. The clinician should therefore aim to engage the individual and understand their opinions on whether they may have an illness and require treatment, rather than challenge them over their beliefs about their illness. People with dementia often lack insight into their cognitive difficulties, and therefore, a collateral history is paramount.

The assessment of capacity is also an essential skill for those working with older people and is discussed in more detail in Chapter 52 and Chapter 58. The Mental Capacity Act 2005 (Department of Health, 2005) clearly sets out the steps involved in the assessment of a person's capacity to make a particular decision at a specific time or in a specific situation. It is assumed that all older adults have capacity to make decisions, unless proved otherwise. The assessment of capacity firstly requires there to be an impairment of the mind or brain. Secondly, there

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needs to be an assessment as to whether any such impairment is sufficient to impair decision-making capacity. Standard questions set out in the Mental Capacity Act are whether the person can: (1) understand relevant information; (2) retain the information (long enough to make a judgment); (3) use or weigh the information; and (4) communicate the decision, ensuring attempts have been made to overcome any sensory or communication difficulties. While the assessment of capacity is a very important skill, as capacity is specific to a particular decision or function, it should only be formally assessed in response to a specific request or question.

Risk assessment

Risk assessment is an important part of the psychiatric assessment of older adults. This includes areas that are common to patients of all ages and more focused areas where individuals with cognitive decline may be vulnerable. Table 9.2 demonstrates possible areas of risk assessment.

Table 9.2 Areas for risk assessment.	
Deliberate self-harm	Risk of self-harm or suicide
Accidental self-harm	Accidental overdose or non-compliance, self-neglect, falls, fire, wandering
Harm to others	Emotional or physical harm, due to aggression, sexual disinhibition, unsafe driving, carer stress, risk to children
Harm from others	Emotional or physical harm, due to violence, elder abuse, financial exploitation
Social and environmental risk	Poor hygiene, cleanliness, hoarding, trip hazards, fire risk, social isolation, loneliness
Physical health risk	Frailty, deterioration in physical health, self-neglect

Deliberate self-harm is less common in older than younger adults, and acts are more likely to represent failed suicide attempts than acts of self-harm (Dennis and Owens, 2012). Older adults may express that they feel they have lived long enough and are ready to die, or wish they would die. However, the belief that life is not worth living should not be considered normative in later life (Van Orden et al., 2015). A detailed exploration of whether any planning or preparations for death have been made (e.g. writing a will, looking up methods of suicide online or in books, speaking

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to euthanasia clinics, stockpiling medication, writing suicide notes) should be made. Following a failed suicide attempt or an act of self-harm, establishing the intent at the time, the perceived lethality, and the timing (e.g. timed to prevent or allow discovery) may help to assess the risk of further attempts.

Accidental self-harm is significantly more common in older than younger people, particularly in those with cognitive impairment. This includes falls, and referral to a local falls clinic for further assessment may be indicated. Lack of compliance or inability to administer medication appropriately can lead to accidental harm, as could unintended self-neglect. Assessment of driving is important for older people, particularly those with a diagnosis of dementia. The DVLA requires that any diagnosis of dementia is reported and patients should be asked if there have been any recent incidents or near misses and ensure that they know of the need to inform the DVLA.

It is important to assess for harm to others. This may be due to physical or verbal aggression, and people with dementia may develop aggressive behaviour, which may precipitate the need for institutionalization (Gilley et al., 2004). Asking an informant whether there have been any incidents of physical aggression is important, as patients with dementia may not recall such incidents. However, they are a significant cause of carer stress and risk and are often challenging to manage.

The assessment of social and environmental risk factors may require a multidisciplinary approach, with occupational therapy or social services assessments providing professional assessment of the environment and any areas that could be addressed.

Physical examination

A brief physical examination is appropriate. If there is any evidence the patient is physically unwell or delirium is suspected, then examination of cardiovascular, respiratory, and gastrointestinal systems prior to referral to colleagues at the general hospital may be indicated. A brief neurological examination of tone, power, sensation, and gait may identify evidence of parkinsonism or stroke. Physical examination is covered in more detail in Chapter 11.

Further assessment

The aim of the initial psychiatric assessment is to formulate a differential diagnosis and prioritize areas that may require immediate action and those that require further assessment. Inpatient admission and assessment may be necessary if there are significant immediate risks or severe behavioural disturbance. If there are no urgent risks identified, further assessment may take place in the community. The use of crisis resolution and home treatment teams for older adults is becoming more widespread and this provides an option for intensive monitoring and assessment in the community; however, the effectiveness of these

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services remains unclear (Streater et al., 2017). It may be appropriate to request an assessment of ADLs or function in the home environment by an occupational therapist. This may help clarify the degree of functional impairment in an individual with early cognitive impairment or could provide an assessment of whether equipment or adaptations to the home could enable a person with dementia to maintain independence or reduce environmental risks.

Similarly, it is often appropriate to refer the patient and family to social services for a care needs assessment or carer assessment. This is important to identify the social care needs of the patient and to access any necessary support, including carers, meals on wheels, and access to day centres, and also to plan for a potential move into residential or nursing care. If there are any urgent concerns regarding safety, vulnerability, abuse, or exploitation, then urgent referral to social services for safeguarding assessment may be necessary.

The medical assessment will usually require further investigations to identify any underlying medical problems that may be causing or contributing to the presentation. As a minimum, blood tests to examine urea and electrolytes, full blood count, thyroid and liver function, and folate and vitamin B deficiencies are required. In many cases, particularly if any abnormalities are detected on neurological examination or if there is cognitive decline, neuroimaging [computed tomography (CT) or MRI] is often appropriate. In cases of borderline cognitive decline or where the differential diagnosis of dementia is unclear, a detailed neuropsychological assessment by a psychologist may be very helpful to identify the pattern and extent of impairment (Jacova et al., 2007).

Principles of management

Having completed an initial assessment, the management plan should develop according to the differential diagnosis and any identified areas of urgent need or those that require further assessment. There are a wide variety of management options open to the old age psychiatrist, based on the diagnosis, urgency, and wishes of the patient and family. The clinician may commence, titrate, and monitor pharmacological treatment or provide or refer for non-pharmacological treatments, including psychological therapy, both of which are discussed in detail in Chapter 13 and Chapters 16, 17, and 18. As in all areas of psychiatry, a holistic approach is paramount, with consideration of the social, functional, and physical needs of the patient as important as psychiatric or psychological management. Perhaps more than in all other groups, liaison with other health care professionals and other agencies, such as primary care, social services, family members, and voluntary agencies, forms a standard part of care. Throughout the assessment and management process, the psychiatrist has an essential leading role using his or her expertise to make key decisions, supervise other team members, and ensure the patient's care is optimally and ethically delivered.

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Clinical cognitive assessment

Chapter: Clinical cognitive assessment

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Introduction

A comprehensive assessment of cognition in the older patient demands a methodical approach, encompassing detailed history-taking from both the patient and an informant with interrogation of the various cognitive domains. In addition, given cognitive symptoms frequently do not occur in isolation, a complete assessment of cognition should also be accompanied by a careful neurological and psychiatric examination.

The forum in which the assessment takes place may influence the extent and focus of the examination; in this chapter, the setting is that of the outpatient 'memory clinic', although many services offer cognitive evaluation in the home setting which can provide context-specific information on functional performance. Assessments of older cognitively impaired patients on acute medical or surgical wards often pose greater logistical challenges, but a broadly similar approach should be feasible. It is crucial, however, to ensure that any such ward-based assessment is not

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confounded by reduced alertness or attention (most typically a delirium, or other types of intercurrent toxic-metabolic encephalopathy). In this case, a reduced assessment is more appropriate, documenting orientation levels and the ability to follow sequential commands as a measure of attention and deferring a more detailed assessment until the patient's baseline is regained (see Chapter 37 for a more detailed exploration of delirium).

History-taking

As a rule, the history of the patient with cognitive symptoms should be taken both directly from the patient, as well as separately from an informant—usually a spouse or close family member. Most well-structured memory clinics request in advance that the patient attends with an informant, and are structured so that each can be interviewed separately and then together. Despite these arrangements, a proportion of patients arrive at such clinics unaccompanied. This can be instructive—attending alone is a powerful predictor of the absence of cognitive impairment and/or the presence of subjective memory complaints (Larner, 2014). However, as always, context is important and an elderly widowed patient attending alone cannot be viewed in the same light as a younger patient in full-time employment who attends without their partner. Hence, as noted earlier, domiciliary visits can be more revealing to clarify the domestic circumstances and provide practical insights into functional abilities.

The history elicited from the patient and informant should begin with broad, open questions, e.g. 'why are you here with us today?', 'are you concerned about your memory?', 'what trouble have you had recently with your memory?'. The questioning strategy should become more targeted, as the information provided begins to yield clues as to the salient cognitive domains affected. Many cognitive clinicians will commence the interview by asking autobiographical questions. These often put the patient at ease and provide some information as to the psychosocial context of the individual, as well as early information on the integrity of long-term memory. Educational and cultural exposure is a key factor in assessing performance on structured cognitive tests. Autobiographical deficits are relatively unusual as a presenting complaint in the memory clinic and most commonly point to one of three possible aetiologies: excessive alcohol use, long-standing poorly controlled temporal lobe seizures, or affective disorders (with or without a psychogenic component).

The patient who presents with established multi-domain global impairments will often pose a challenge in terms of accurate classification, but establishing the first cognitive domain affected from the informant usually has considerable value in distinguishing the diagnostic phenotype. Using broad categories, caregivers can usually quite readily identify which of memory, language, visual function, or behaviour disturbance was the first to become evident. Some features

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which can be helpful in distinguishing the aetiology of cognitive disturbance are listed in Table 10.1.

Table 10.1 Discriminating features in common neurodegenerative diseases		
Disease	History	Clinical findings
Alzheimer's disease	Repetition of the same question with rapid forgetting of the answer Getting lost on familiar routes	Disproportionate deficits in categorical > letter fluency Amnesic deficits that do not improve with cueing
Frontotemporal dementia (FTD)		
Behavioural variant (bv)	Loss of empathy Eating changes Rigid behaviours and stereotypies Social inappropriateness Disinhibition Lack of insight	Poor rapport-forming with examiner Concrete abstraction Deficits on Frontal Assessment Battery
Semantic dementia	Difficulty with naming objects Inability to understand meaning of words	Fluent, but empty, speech Poor word recognition Surface dyslexia
Progressive non-fluent aphasia	Mispronunciation of words New or recrudescant stammer	Agrammatic, telegraphic speech Difficulty with repetition of multisyllabic words Orobuccal apraxia (e.g. cannot whistle or yawn to command)
Logopenic aphasia (often underlying AD pathology)	Slow speech and difficulty with naming objects	Prominent anomia and word-finding pauses Impaired sentence repetition

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	Longer sentences are not understood	
Frontotemporal dementia with motor neuron disease (FTD-MND)	Rapid progression of a behavioural syndrome and/or language deficits, often with prominent delusions and/or hallucinations (transient)	Muscle atrophy Fasciculations (limb or tongue) Spastic or nasal speech Focal weakness
Progressive supranuclear palsy (PSP)	Falls (often retropulsion) Profound apathy and/or impulsivity Slowed movement and thinking	Frontalis overactivity Axial rigidity, retrocollis Slow vertical saccades or vertical gaze palsy Loss of postural reflexes
Dementia with Lewy bodies	Visual hallucinations Fluctuating cognitive ability Falls, tremor REM sleep behaviour disorder	Mild parkinsonism Disproportionate visuospatial dysfunction
Corticobasal syndrome	Difficulty using objects with one hand Limb having 'a mind of its own'	Limb apraxia Stimulus-sensitive myoclonus Parkinsonism May develop non-fluent language syndrome
Huntington's disease	Family history (autosomal dominant) of movement disorder or prior psychiatric diagnoses or suicidality	Generalized chorea
Vascular dementia	Vascular risk factors	Pyramidal signs

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	May have stepwise decline, but frequently do not	
Creutzfeldt-Jakob disease (CJD)	Rapid cognitive decline Neuropsychiatric features Movement disorder	Ataxia, tremor, myoclonus
Normal pressure hydrocephalus	Gait deterioration Slow cognitive processing Urinary incontinence	Apractic magnetic gait Hyperreflexia

Memory

The patient with typical anterograde episodic amnesic impairment may struggle to illustrate their difficulties with examples, as opposed to the patient with subjective cognitive complaints who can provide detailed examples of what they perceive as memory failure. An attempt should be made to distinguish true medial temporal 'rapid forgetting' from working memory failures where attentional components are more at play. In the latter, patients will retrieve the missing information or item, or at least recognize it when re-presented, unlike the patient with amnesic mild cognitive impairment (MCI) who may not. In the truly amnesic patient, the accompanying informant will frequently volunteer examples of rapid forgetting and repetitive questioning, into which the patient may have limited insight. In day-to-day life, the informant may report that the patient who enjoys television viewing can no longer recall or 'follow' the plots of soap operas or movies, or that an erstwhile sports fan cannot remember the outcomes of important sporting encounters, minutes or hours after watching them.

It is important to gauge the extent of functional impact of the reported amnesic symptoms. This can be broached by asking if important appointments/engagements have been missed; if there has been repeated difficulty recalling PIN numbers for banking cards; and if there have been episodes with safety implications such as inadvertent repeat dosing, or omission of, medications or failure to turn off electrical appliances, etc. Difficulties in managing finances (less easy to identify in the era of direct debits) or keeping up-to-date with car taxing and insurance dates may be identified. Many patients with preserved insight in the early stages of an amnesic cognitive syndrome will begin to use memory aids such as lists or written or electronic reminders. Functional impairment can be more difficult to establish where the informant or other family members have always, or more latterly, assumed some of the responsibilities of the patient (e.g. the doting spouse or son/daughter who insists on laying out

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clothing for the older patient, preparing their meals, and generally running the household) and/or where this is downplayed due to fear of a negative diagnosis.

Visual memory is important to explore also—topographical disorientation (TD), such as route-finding difficulties in familiar localities, is a sensitive marker for possible parieto-occipital degeneration and may be a harbinger of the posterior cortical atrophy (PCA) variant of Alzheimer's disease (AD) or dementia with Lewy bodies (DLB). The neuroanatomical basis of TD is complex but is largely felt to derive from a failure to access stored allocentric spatial memory, along with landmark agnosia.

Prosopagnosia—the inability to recognize familiar faces—is a rarer finding, implicating the ventral occipitotemporal 'what' visual pathways and should not be confused with the relatively innocuous phenomenon of being 'unable to put a name to a face'. Prosopagnosia can have quite dramatic manifestations with patients not recognizing close family members, or even their own reflection in the mirror, i.e. the so-called 'mirror' sign. This can, in turn, overlap with, or develop into, delusional misidentification.

Executive function

Executive function is an umbrella term that encompasses a set of higher-order processes (such as inhibitory control, working memory, and attentional flexibility) that govern goal-directed actions and adaptive responses to the environment. Dysfunction in this cognitive domain may be elicited by enquiring into the patient's ability to plan ahead, remain focused on a task to hand, and/or multi-task. Speed of cognitive processing is also of relevance. Informants will often report that the patient with executive dysfunction can successfully accomplish single tasks if uninterrupted by other demands on their attention but struggles if more than one stimulus is presented. Difficulties of this nature reflect impairments in dorsolateral prefrontal cortex function. In more advanced cases, patients with executive dysfunction lose cognitive flexibility and can become very rigid in their thinking, with a narrowing in their behavioural and motor repertoire. This can be distinguished from obsessive-compulsive disorder by the lack of insight held by the patient. Poor judgment, e.g. while driving, can be reported; alternatively, caregivers may report uncharacteristic vacillation/indecisiveness. Loss of inhibitory control (indicative of orbito-frontal dysfunction) can lead to marked behavioural change: poor table manners and other faux pas in social etiquette (e.g. skipping a queue), inappropriate jocularity or over-familiarity, or sexually inappropriate themes or behaviours. Loss of inhibitory control can also become evident in dietary behaviours—patients can develop an incorrigible 'sweet tooth' and have limited awareness of satiety, with hyperphagia and food cramming behaviours. An extreme manifestation is hyperorality, with oral exploration and sometimes consumption of inedible objects. With anterior cingulate dysfunction, empathy and interpersonal warmth may be lost, sometimes superseded by cold and callous behaviour. In other respects, the patient

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may become apathetic and uninterested in themes previously of importance to them, e.g. the previously immaculately attired individual who loses all interest in grooming and personal hygiene. Apathy is also strongly associated with frontostriatal dysfunction. With frontal lobe lesions, impulsivity can also emerge—characterized by the patient ‘acting before thinking’; this is particularly striking in the motor impulsivity seen in progressive supranuclear palsy where the patient jumps to the standing position from his seat only to retropulse backwards again due to postural instability—the ‘rocket’ sign.

Language

Patients and families relatively rarely volunteer language as a difficulty, but on careful questioning and observation of the patient’s spontaneous speech, it can become apparent that what was perceived as a ‘memory’ problem is, in fact, a disorder of language. While formal, prescriptive examination of the various elements of speech has a useful diagnostic value, much can be gleaned in the office by simple interaction with the patient. The patient’s fluency and their ability to understand the content of speech and its prosody are instructive. Paraphasias (incorrect word substitutions) should also be noted—phonemic errors, such as ‘dork’ for ‘fork’, or semantic errors such as ‘brother’ for ‘husband’.

Slow, faltering, effortful speech with long word-finding pauses, producing a low output of words per minute—often with phonemic errors—is suggestive of a progressive non-fluent aphasia (PNFA). As this syndrome advances, grammar becomes parsimonious with omissions of conjunctions, prepositions, definite or indefinite articles, etc., although the intended meaning of speech is usually still conveyed. This is often referred to as ‘telegrammatic’ speech. For example, a patient who wishes to say ‘close the door as it is cold’ may only manage to utter ‘close-door-cold’. Patients can also have immense difficulty with repetition of multisyllabic constructs, e.g. ‘unintelligible’ or ‘caterpillar’. Many of these patients also have a demonstrable orobuccal apraxia, which is a deficit in use of the lips, tongue, and pharynx to perform skilled, learnt motor tasks such as mimicking how to blow out a candle or suck through a straw. Comprehension, for single words at least, is spared, although the patient may struggle with comprehending instructions with increasing syntactic complexity.

Another aphasia variant is the logopenic aphasia characteristic of AD. These patients demonstrate preserved grammatical structure and, as such, seem relatively fluent, but production rate is slow and speech is punctuated by long, dramatic pauses as they search for single words, often mid sentence. Compensatory strategies, such as circumlocution (attempts to describe the relevant word by other means, e.g. ‘the thing for digging’ for spade) or supraordinal substitution (e.g. ‘bird’ for ‘owl’), are often employed. While single-word repetition is relatively spared, repetition of sentences is impaired, in keeping with the theory that the

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mechanism for the syndrome is one of a phonological short-term memory deficit (Gorno-Tempini et al., 2011).

Semantic failure is an even more striking form of language dysfunction. The patient's comprehension of the intrinsic meaning of a word is altered, which can rapidly become disabling. In tandem with this, confrontational naming is impaired. The patient will often fare no better when presented with non-verbal cues (e.g. visual, tactile), i.e. they present with semantic memory failure beyond language alone. This underscores a more universal decline in conceptual knowledge. For example, a patient may no longer recognize the purpose or function of a tool or implement, e.g. a corkscrew or nail clippers. Reading may be characterized by surface dyslexia, whereby native English speakers do not recognize irregularly pronounced words, particularly those of lower frequency usage, e.g. they may read 'sew' as 'su' or 'dough' as 'doog'; the error presumably arises as the patient has lost the semantic context of the word. Each of these aphasia syndromes is associated with abnormality in specific cortical areas: the left posterior frontal and insular regions in PNFA; left posterior perisylvian or parietal atrophy in logopenic aphasia; and the (left) anterior temporal lobe in semantic aphasia. See Table 10.2 for some useful clinical pointers in approaching the patient with aphasia.

Table 10.2 Tasks that may be used to assess speech and language functions in primary progressive aphasia.

Speech/ language function	Task	Behavioural measures	Variant in which impaired
Speech production			
Grammar	Picture description task; story retelling (e.g. picture aided); constrained syntax sentence production task	Grammatical structure; mean length of utterance; speech rate; accuracy of content; melody; prosody; specific error types in word selection; articulation	Non-fluent/agrammatic variant
Motor speech	Motor speech evaluation, including	Effort; hesitations; presence of	Non-fluent/agrammatic variant

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	multiple repetitions of multisyllabic words; diadochokinesis of speech articulators; spontaneous speech	apraxia of speech or dysarthria; specific types of speech sound errors; factors that affect articulation (e.g. word length in syllables)	
Confrontation naming	Single-word retrieval in response to pictures, sounds, foods, and odours	Error rate; delay in naming; factors that affect naming accuracy (e.g. familiar versus unfamiliar items, nouns versus verbs, semantic category); error types (e.g. semantic errors, phonemic errors)	Severe deficit in semantic variant with semantic errors; moderate impairment in logopenic variant with phonemic errors
Repetition	Oral repetition of words, pseudowords, phrases, and sentences	Factors that affect repetition accuracy (e.g. predictability of the phrase, sentence length, grammatical complexity); error types	Logopenic variant with phonological errors
Sentence comprehension	Matching orally presented sentences to pictures; answering yes/	Factors that affect comprehension (e.g. grammatical	Non-fluent/agrammatic variant, effect of grammatical complexity;

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	no questions; following directions	complexity; reversibility of the sentence, e.g. 'The boy was kicked by the girl' versus 'The ball was kicked by the girl')	logopenic variant, length, and frequency effect
Single-word comprehension	Word-picture matching; word-definition matching; synonym matching	Factors that affect comprehension (e.g. familiarity; frequency; grammatical word class)	Semantic variant
Object/people knowledge	Picture-picture matching; odd- one-out; semantic associations; gesture-object matching; sound-picture matching	Factors that affect object knowledge (e.g. familiarity, semantic category)	Semantic variant
Reading/ spelling	Lists including regular and irregular word lists, from various word classes, matched for other factors; pseudowords matched to words in length	Factors that affect reading/ spelling accuracy (e.g. regularity, frequency, word class); error types (e.g. regularization, phonologically plausible errors, articulatory distortions)	Semantic variant with 'regularization' errors; logopenic variant with phonological errors

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Classification of primary progressive aphasia and its variants.

Visuoperceptual function

Visuospatial dysfunction may be quite subtle in its presentation. The archetypal higher-order visual syndrome in the memory clinic is Balint's syndrome, typically indicative of PCA. PCA is most often a manifestation of Alzheimer pathology, but DLB, corticobasal degeneration, and, more rarely, prion disease can underlie this presentation. Patients with PCA can present with myriad visual symptoms (Box 10.1) and frequently have spent a considerable period of time with ophthalmological assessments or even have a functional psychiatric diagnosis before the true diagnosis is determined. The full classical triad of optic ataxia, oculomotor apraxia, and simultanagnosia is rarely seen in practice, but these signs should be sought. Optic ataxia refers to an inability to accurately identify the spatial location of a visual cue in the peripheries, in spite of normal visual fields; it is ameliorated when an acoustic cue is added (e.g. the examiner holds a set of car keys within the patient's field of vision and asks them to point to them; they cannot perform this or do so with faltering, searching movements—localization of the target improves dramatically when the examiner jangles the keys). Oculomotor apraxia refers to an apparent inability to direct conjugate gaze to a target on command, in spite of the presence of a full range of extraocular movements, when completing a spontaneous visual search. Simultanagnosia is the phenomenon where a patient cannot appreciate a visual scene in its entirety, e.g. the 'Boston Cookie Theft' scene is described piecemeal, and not seen as a whole. Another test to elicit this is to place a number of items in the patient's field of view and ask them to describe what they see—the patient with simultanagnosia will describe one item only, yet can identify each of them when presented individually. Clinical clues to the presence of an emergent PCA syndrome include left/right disorientation and dyscalculia, which are also dominant parietal lobe functions which may accompany Balint's. The latter can be elicited by enquiring into how readily and accurately a patient can manage simple arithmetic such as small cash transactions, or if there is a history of difficulty with interpreting numbers such as display prices, pinpads, or mobile telephone keypads.

Box 10.1 Visual manifestations of posterior cortical atrophy

- Glare sensitivity
- Simultanagnosia
- Optic ataxia
- Optic apraxia
- Visual field deficits

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- Complex visual hallucinations
- Impaired depth perception
- Impaired contrast sensitivity
- Alexia
- Visual crowding
- Prosopagnosia
- Palinopsia
- Achromatopsia
- Prolonged colour after images
- Visual disorientation
- Reverse-size phenomena
- Mirror sign
- Illusion of movement of static objects
- Akinetopsia
- 180° upside-down room tilt illusion

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Less ‘canonical’ visuoperceptual symptoms can often manifest in DLB and AD. An enquiry into driving accuracy can frequently be instructive—a litany of clipped kerbs, near misses, or minor road traffic accidents can be disclosed, or sometimes, tellingly, a loss of parking accuracy. Some patients will acknowledge subjective concerns and will have spontaneously curtailed journey lengths and frequencies, but a caregiver estimation of safe performance is much more reliable and robust (Iverson et al., 2010). Dressing apraxia is another indicator of visuoperceptual dysfunction—the patient has been observed to place clothing on inside-out, or back-to-front.

Other cortical visual symptoms can include positive phenomena such as palinopsia (persistent perception of a visual image despite its physical removal from the visual field) and cerebral polyopia (single targets perceived as multiple). Visual hallucinations should be directly enquired about—complex, recurrent visual hallucinations are almost pathognomonic of DLB, in the absence of retinal disease. Sometimes caregivers will be astonished to hear the patient endorse the experience of visual hallucination, as they may not have volunteered it before. Frequently, the hallucinations of DLB are well formed of people and animals; the patient will often recognize the individuals. Insight is preserved and the experience—typically, but not universally—is not

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distressing. A *forme fruste* of visual hallucination (which is usually spontaneous, in the absence of a visual stimulus) is pareidolia. These are visual misperceptions of a visual stimulus, such as attributing animate characteristics to an inanimate scene, e.g. perceiving a face in a carpet or wallpaper pattern. Even more subtle can be the 'sense of passage' experienced as a prelude to more frank hallucinatory experiences in DLB—the patient reports a sense of someone having 'passed by' an adjacent window or 'passed just over the shoulder' where no such stimulus existed. These experiences of a sense of passage or presence are sometimes referred to as 'extracampine' phenomena and may also feature in Parkinson's disease.

Auditory cognition

Less well explored as part of the cognitive assessment is the domain of auditory cognition, but it merits some attention. Many patients and their caregivers will attribute some, or all, of their cognitive difficulties to poor hearing. Hearing loss in itself is significant to identify as it has been shown to be independently associated with incident all-cause dementia (Lin et al., 2011) and older adults with hearing loss are at greater risk of dementia than those with normal hearing (Davies et al., 2017). The mechanisms by which hearing loss may contribute to cognitive decline remain to be elucidated. Assessing for a higher-order 'central' contribution to the perceived hearing difficulties can be difficult, but some clinical pointers may include difficulty with understanding speech versus other sounds, recognizing familiar voice or music, or difficulty locating sounds generated in the same room (Hardy et al., 2016).

Praxis

Apraxia refers to difficulty in execution of skilled, purposeful movements, in the absence of weakness or sensory or comprehension deficits. Apraxia has several potential neuroanatomical correlates, but the dominant inferior parietal and prefrontal regions are most commonly implicated. Patients and informants will often allude to their difficulties as 'disorientation' or 'lack of coordination'. On careful history-taking (and examination), however, it will become apparent that the symptoms described are, in fact, higher-order cortical problems. Useful questions to elicit apractic symptoms include enquiry as to loss of skills using tools and household equipment, e.g. microwaves, dishwashers, or remote control units for TVs. Such difficulties can, of course, overlap with executive dysfunction. In the last decade, a useful line of questioning relates to loss of skills required to use a mobile telephone or computer; informants will often report inaccurate text messages or, quite tellingly, that the patient has withdrawn entirely from the use of modern technological devices. In each case, it is important to ascertain, insofar as possible, any visual contribution to these difficulties, underscoring the need for a careful neurological examination. Patients with apraxia will often have insight into their difficulties, particularly where there is a focal apraxia of a limb such as that seen in the corticobasal syndrome—the

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patient will frequently report 'it just doesn't do what I want' and are frustrated at their poor ability to execute or mime movements. An extension of this is the rare manifestation of lesions of the supplementary motor area and/or the corpus callosum in the form of alien limb phenomenon. The affected limb is apractic, with reflexive grasping, and can appear to levitate or move autonomously, most dramatically with intermanual conflict. In some cases, the patient can fail to recognize the limb or even deny ownership of it.

Time course of symptoms

Having clarified whether there are specific cognitive symptoms, it is important to establish the rate of symptom progression.

Neurodegenerative processes, such as AD, DLB, and frontotemporal dementia (FTD), generally progress insidiously over years, although more aggressive phenotypes are recognized (Gaig et al., 2011; Lee et al., 2017; Schmidt et al., 2011). Static symptoms are more indicative of a fixed structural deficit (e.g. after a stroke or an acquired brain injury) or can be a feature of the 'worried well'. Static behavioural symptoms over serial assessments, in the absence of functional impairment, in a patient suspected of FTD raises the possibility of the FTD phenocopy, an increasingly recognized entity typically seen in younger patients and often presenting with underlying comorbid psychiatric features, but lacking in any overt progressive neurodegenerative changes on serial imaging (Gossink et al., 2016).

A stepwise progression in symptoms is supportive of a vascular aetiology, or at least a contribution, to the presentation. Fluctuating symptoms raise a number of possibilities, and diurnal fluctuation should be specifically enquired after, as this is highly suggestive of DLB (McKeith, 2002). Where there are pointers in the history towards fluctuating cognition, this can be quite easily assessed by means of a simple four-point questionnaire (Ferman et al., 2004). Delirium is perhaps the most dramatic manifestation of fluctuating alertness and attention, and a prodromal history of apparently easily precipitated, frequent, or prolonged delirium should bring DLB to the fore of the clinician's mind (Jicha et al., 2010; Vardy et al., 2014). More prolonged periods of fluctuation, over weeks to months, raise the possibility of autoimmune or metabolic encephalopathies.

Other neurological symptoms

As cognitive dysfunction is frequently accompanied by other neurological symptoms, it is important to assess for these. In particular, motor symptoms are important to elucidate, as patients with extrapyramidal disorders and motor neuron disease (MND) can present with early prominent cognitive symptoms to the memory clinic. A large prospective study identified that almost 14% of patients with MND satisfied diagnostic criteria for FTD at diagnosis; a further 34% had deficits on cognitive testing, predominantly in frontal-executive function (Phukan et

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al., 2012). It is not unusual for some of these patients, particularly those with salient language deficits, to be referred in the first instance to a memory clinic, before motor symptoms become overt. Up to 20% of patients with the atypical parkinsonian disorder progressive supranuclear palsy (PSP) present with a frontal lobe behavioural syndrome, before classical motor features are evident (Donker Kaat et al., 2007). While overt parkinsonism in DLB is easy to identify, in practice, it may be quite subtle, or indeed absent, in the early disease stage, and there is a poorly quantified proportion of patients who receive an autopsy diagnosis of DLB without ever having manifested clinically evident (or perhaps clinically recognized) extrapyramidal features (Savica et al., 2013). Patients should be asked about tremor, stiffness, slowing up in execution of movements, and balance and gait changes. Useful clinical questions include: enquiring about speed of dressing, slowness and discomfort on turning over in bed, size and legibility of handwriting, change in posture (caregivers will frequently endorse this—identifying a more anteroflexed posture and more rounded shoulders), and speed of walking. Useful, validated toolkits have been published which can aid the non-movement disorder expert in the assessment of patients with suspected DLB (<https://research.ncl.ac.uk/diamondlewy/assessmenttoolkits/>).

Unexpected and/or frequent falls should also raise the possibility of an extrapyramidal or other motor disorder in the mind of the cognitive specialist. Weakness, particularly focal and insidious weakness, may herald a pyramidal or an amyotrophic process such as MND. The patient should be asked about muscle cramps, frequently an early feature of denervation in MND, and about respiratory symptoms indicative of evolving respiratory muscle weakness such as dyspnoea on minimal exertion and orthopnoea (intolerance of lying flat). Similarly, early bulbar symptoms, such as altered speech intelligibility or dysphagia, imply a more diffuse process than cortical dementia alone and should prompt consideration of an associated amyotrophic or atypical parkinsonian process. Weight loss is associated with the advancing stages of all neurodegenerative diseases but is particularly striking in MND, in which it can be an early feature, presaging many of the classical motor features. The mechanisms for this are poorly understood; it may be due to an innate hypercatabolic state associated with the disease process (Korner et al., 2013) and is often in excess of the extent of any dysphagia which is present.

If motor deficits are described as occurring in an abrupt and/or a stepwise fashion, consideration needs to be given to a potential vascular contribution to cognitive symptoms. Cognitive symptoms emerging simultaneous with an acute-onset neurological deficit should prompt an exploration of the history to ascertain the extent, if known, of cerebrovascular disease and other vascular risk factors. The contribution of macrovascular and microvascular cerebral disease to cognitive impairment and to the clinical picture of AD has long been recognized

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and a history of stroke, transient ischaemic attack, hypertension, dyslipidaemia, and/or diabetes should be checked for.

Hyposmia is a robust predictor of α -synucleinopathy (and hence DLB). This lack of perception of odour is qualitatively different from the preserved perception of, but poor ability to *discriminate*, odours seen in patients with early AD. Autonomic dysfunction, such as postural dizziness, marked urinary sphincteric dysfunction, constipation, or erectile failure in men, may also support an incipient DLB process. While a pattern of irritative lower urinary tract symptoms emerging in tandem with cognitive symptoms is a relatively common and non-specific picture (often reflecting the coincidental higher prevalence of both symptoms in older people), it should raise the possible differential diagnosis of normal pressure hydrocephalus in the clinician's mind, especially if there are associated gait difficulties and/or lower limb parkinsonism.

Sleep and cognition

It is crucial to assess sleep quality, both in the patient's estimation and that of the bed partner, if relevant. Poor-quality sleep is increasingly recognized as a harbinger of amnesic cognitive impairment and AD (Blackwell et al., 2014; Lim et al., 2013). Whether this is a prodromal marker of neurodegeneration, or a contributor to it, remains hotly debated. Hypersomnolence (excessive daytime somnolence) is a supportive feature in the DLB diagnostic criteria. This symptom merits further enquiry, as fragmentation of nocturnal sleep from obstructive sleep apnoea or periodic limb movements of sleep may be contributory and can be easily remediated. Parasomnias can be divided into rapid eye movement (REM) sleep behaviour disorder (RBD) and non-REM sleep parasomnias. The former can usually be identified quite readily from questioning of the bed partner who will describe dream enactment behaviour. The typical account is one of purposeful, often violent, movements which can result in injury to either the patient or the bed partner. Loud vocalization usually accompanies the motor phenomena. The patient can usually be roused easily and will classically describe dreams with violent or threatening themes. Notably, the aggressive nature of the dream enactment is often at odds with the patient's waking personality. RBD tends to manifest most reliably in the second half of the night, since the proportion of time spent in REM sleep accumulates overnight. The presence of RBD is highly predictive of incipient α -synucleinopathy—91% of patients with the syndrome develop a neurodegenerative disease over long-term follow-up, almost invariably with α -synuclein pathology (Iranzo et al., 2014).

Other psychiatric symptoms

An important component of the cognitive assessment is the elucidation of affective symptoms which may underlie some, or much, of the patient's reported difficulties. This can be done both in a qualitative fashion by direct enquiry into symptoms of anxiety and depression, and semi-

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quantitatively by use of self-completed questionnaires such as, *inter alia*, the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983), a simply administered and widely validated tool for the identification of affective symptoms. Abnormally high scores in either the depression or anxiety scales should alert the cognitive clinician to a possible contributory role for these symptoms in either the presentation of the patient or their subsequent cognitive test performance. Both anxiety and low mood affect attentional capacity and working memory; in this context, the concept of ‘depressive pseudodementia’ has long been recognized as a manifestation of mood disorders, dating back to descriptions of ‘melancholic dementia’ of the nineteenth century. However, one must be cautious about blithely attributing all cognitive symptoms purely to mood disturbance, particularly in the older patient cohort; learning and memory deficits in the presence of depression predict evolution into dementia over time in older cohorts (Heser et al., 2016). Furthermore, later-life depression is widely recognized as a harbinger of neurodegenerative disease; older patients demonstrating neuropsychiatric symptoms, such as apathy, depression, irritability, agitation, and night-time behavioural disturbance, have a higher risk of subsequent MCI (Geda et al., 2014), while anxiety, depression, and apathy are validated supportive clinical features in the diagnosis of DLB (McKeith et al., 2017). As such, follow-up of older patients who present with cognitive symptoms in the setting of a mood disorder is appropriate, with reassessment once affective symptoms have been effectively treated.

Psychotic symptoms accompanying cognitive impairment are important to identify as they may have diagnostic significance, as well as being a source of considerable morbidity in their own right. The well-formed, frank visual hallucinations associated with DLB have been discussed earlier; the patient typically has insight into the unreality of these visions, at least early in the disease trajectory. Hallucinations in other modalities can occur in DLB and sometimes are underestimated in the clinic—in particular, auditory and haptic (hallucinations of touch). Hallucinatory symptoms are not specific for DLB; they can accompany other neurodegenerative conditions but are less commonly seen in the earlier stages. Delusions and paranoid ideation are further neuropsychiatric symptoms encountered not infrequently in the memory clinic. Delusional phenomena can vary from mood-congruent nihilistic delusions in the depressed older patient to more discrete classical syndromes such as Capgras syndrome (where the patient believes a spouse or other loved one has been replaced by an imposter) and ‘phantom boarder’ syndrome (where the patient believes that someone else lives, uninvited, in their home). Reduplicative paramnesia is the term appended to a belief held that a location (most commonly, the home) has been duplicated and exists in two places at once. There continues to be a debate as to whether the latter syndromes constitute truly delusional experiences or are misidentification phenomena due to perceptual dysfunction. Othello syndrome refers to pathological jealousy experienced by the patient who believes their spouse is being unfaithful; there is some evidence (and

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clinical experience would suggest) that the latter is much more commonly seen in DLB than AD or other dementias (Hashimoto et al., 2015).

Psychotic symptoms traditionally were considered rare in FTD; in recent decades, however, there has been recognition of a prevalence rate of approximately 10%, with a particular preponderance in patients carrying mutations in *C9ORF72* and *GRN* (Shinagawa et al., 2014).

Background medical history

As in any clinical assessment, it is important to take a detailed background medical, surgical, and medication history. Stroke, liver disease, malignancy, or chronic pain syndromes, among others, may be highly relevant. Polypharmacy is frequently encountered in the older patient cohort and numerous centrally acting medications (which may be prescribed for mood, pain, or sleep) can impact cognition. High-potency opioid transdermal patches can often be overlooked as relevant components of the medication history by patients and caregivers. Other contributors may be less obvious—it is important to be mindful of the potentially deleterious effects of drugs with anticholinergic effects or of the cumulative effects of some older anticonvulsants on cognition in patients with long-standing epilepsy.

Family history and genetics

Family history is of great relevance in the assessment of a young-onset dementia patient but may be perceived by some as of less importance in a patient presenting over the age of 65. However, this is not strictly true. A patient with one parent diagnosed with dementia under the age of 80 has double the chance of developing dementia themselves (Wolters et al., 2017). This is likely attributable to polygenetic and other factors, since familial autosomal dominant (Mendelian) AD is very rare in this age group, with a <1% chance of identifying a causative Mendelian gene, even with two affected first-degree relatives over the age of 65 (Loy et al., 2014). FTD, however, is a much more familial entity, and an assiduous family history should strive to elicit other potential presentations of FTD or its causative gene. There may be a family history of family members, for example, having been institutionalized for unclear reasons, suffering from apparent alcoholism, or receiving diagnoses of schizophrenia, MND (with and without dementia or behavioural disturbance), or dementia attributed to other causes such as AD or vascular dementia. Two genes associated with FTD can have highly variable age of onset and penetrance—*C9ORF72* and *GRN*—and thus may merit consideration if a multigenerational family history of dementia or other behavioural problems emerges.

Social history and driving

The social history is key to contextualizing the patient's symptoms; the nature of their home and family supports and the physical context of the domestic environment are important practical pieces of information. A

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domiciliary visit can provide valuable insights into these aspects. Alcohol intake, smoking, and recreational drug use should not be overlooked in the memory clinic, particularly the former. Increasing evidence points to a role for alcohol in hastening cognitive decline (Bos et al., 2017). Diet may be relevant, as up to 11% of patients over 65 years have clinically relevant deficiencies in vitamin B12 levels (Lindenbaum et al., 1994), with its attendant negative effect on cognitive performance. Educational exposure and occupation are also key pieces of information, as they will colour the interpretation of subsequent formal cognitive testing. If not already established in the assessment of functional impact of symptoms, it is also crucial to enquire at this point as to whether the patient drives or not. This important piece of information may have significant medicolegal implications (see Chapter 57 for a detailed discussion of driving and dementia).

Cognitive examination: quantitative and qualitative assessments

A detailed patient and informant history will already have provided much qualitative information as to the cognitive syndrome at play. It is then important to examine the cognitive domains in an objective, standardized, and semi-quantitative manner. A multitude of bedside cognitive assessment tools exist; probably the most widely used in English-speaking countries are the Mini-Mental State Examination (MMSE) (Folstein et al., 1983), the Test Your Memory (TYM) (Brown et al., 2009), the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), and the Addenbrooke's Cognitive Examination (ACE) (Mioshi et al., 2006). The choice of assessment tool will depend on the circumstances; broadly speaking, the first three are effective screening tools but may not be adequately challenging, or sufficiently comprehensive, to detect subtle abnormalities. Certainly, the MMSE is a relatively blunt instrument, biased towards attention and mnemonic function, with little or no interrogation of frontal/executive function and limited language and visuospatial testing. It is prone to ceiling effects in early-stage cognitive syndromes and in those with significant educational exposure. The TYM incorporates more cognitive domains and is more robust than the MMSE in correlating with the outcomes of full detailed neuropsychological assessments (Koekkoek et al., 2013). A unique feature of the TYM is its ready self-administration and, as such, it is often effectively utilized in screening out subjective cognitive complaints in a time-pressured general neurology or psychiatry clinic, rather than as a semi-quantitative tool in a dedicated memory clinic. The MoCA is also more encompassing than the MMSE, but again it is better considered as an effective screening tool than providing a thorough, quantitative assessment. These tools are available in a multitude of languages, and normative data have been published.

The ACE (now in Version III) is perhaps the most detailed multi-domain bedside cognitive assessment tool used by cognitive clinicians. It is important to remember that bradyphrenia, perseveration, intrusions, apraxia, anxiety, or indifference cannot be conveyed on scoresheets but

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are important to consider in the interpretation of any cognitive assessment, and the presence of these should be highlighted in a commentary on the test scoring. Similarly, motor and sensory impairments can influence performance and their presence should be noted. The ACE is scored out of 100, with subscores for attention, memory, fluency, language, and visuospatial function. Even within subscore, it is important that the clinician is aware of the 'flavour' of the deficits; for example, poorer performance in categorical (semantic) fluency than in letter fluency is indicative of an impaired search strategy, more in keeping with a medial temporal pathology, whereas impaired letter fluency implies executive dysfunction. An analysis of how patients reach their final score in memory is also important; for example, a significant improvement in the name-and-address recall item score with cueing is supportive of a dysexecutive retrieval problem than an encoding difficulty. One of the few weaknesses of the ACE is the absence of a test of visual memory; this can be performed by administration of the Rey-Osterreith complex figure or by using additional, bespoke, tools.

If time permits, deficits in any one or more domains should be explored further. For example, patients who appear to have prominent frontal dysexecutive features on the ACE should ideally also complete the Frontal Assessment Battery (Dubois et al., 2000), which incorporates tests of inhibitory control, set-shifting, and abstraction. The patient with frontal lobe dysfunction may not be able to conceptualize similarities between a table and a chair beyond their wooden nature or see beyond 'wheels' as a unifying theme linking a train and a bicycle. As the level of abstraction increases, they may flatly declare that there are no common themes, e.g. between a watch and a ruler. Similarly, patients can be asked to interpret common proverbs (e.g. 'too many cooks spoil the broth' or 'people in glasshouses shouldn't throw stones') for evidence of concrete thinking; however, this is probably only reliably interpretable in patients with a reasonable premorbid educational exposure and such tests can be very culturally specific. Another useful line of enquiry is the concept of cognitive estimates; for example, a patient is asked 'how many lions are in Dublin?'—the frontal patient may produce a bizarre or a highly inaccurate response. A simple test to unveil perseveration is the 'signe d'applause', wherein the clinician instructs the patient to copy precisely what he is about to do; the examiner claps three times. Patients with frontal dysfunction will clap several more times, often until they are instructed to stop.

Prominent amnesic dysfunction can be explored in more detail by asking the patient to relay recent current affairs or sporting news items of which they are aware. The amnesic patient will frequently engage in a certain amount of 'provoked confabulation' at this juncture. Retrograde memory will also be affected in neurodegenerative syndromes. Patients can be asked about landmark political, sporting, or natural or manmade disasters, e.g. general election or referendum results, the Olympic Games, World Cup competitions, extreme weather events, terrorist

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attacks, etc. Typically one establishes a temporal gradient, with better preservation of more distant memories than more recent ones ('Ribot's law'). Sudden retrograde memory loss, the absence of a gradient, or an abrupt, precise cut-off point in time, with or without autobiographical memory loss, is often indicative of psychogenic or functional amnesia. One should also conduct tests of visual memory and recognition, e.g. the 'familiar' and 'unfamiliar' faces test of the Queen Square 'Green Book', with the former depicting well-known cultural figures and the latter a series of four previously unseen male faces, whom the patient is then asked to recognize from a panel of nine faces after a brief delay.

Language and visuospatial deficits elicited on the ACE can also be further explored with ancillary bedside tests. An assessment of reading, both comprehension of a written instruction (e.g. 'close your eyes') and verbal reading output (e.g. the passage from the Queen Square 'Green Book' or the Rainbow Passage), should be conducted where deficits in one or both of these domains are apparent.

The ACE does not incorporate definitive tests of praxis, but apractic attempts at cube and clock drawing can be observed. Formal tests for apraxia should be conducted as part of a complete neurological examination (see General neurological examination, column opposite), particularly if a prominent flavour of parietal deficit emerges from the history.

A cut-off score of 88 on the ACE is very sensitive for dementia, but at the cost of specificity; the converse is true for a cut-off of 82, increasing the chances of missing bona fide dementia cases. The Test Your Memory for Mild Cognitive Impairment (TYM-MCI) is a short, easily administered assessment tool, with visual and verbal recall aspects designed to optimize detection of amnesic MCI (aMCI)/AD. It is of particular utility for those patients with equivocal ACE scores (i.e. between 83 and 87) where there is suspicion of an evolving aMCI/AD process (Brown et al., 2017). Visual memory is affected early on in AD but is not routinely tested on many bedside cognitive assessment scales.

Neuropsychology and occupational therapy

Trainees and non-specialists often have the impression that access to specialist neuropsychology is necessary to run an effective memory clinic. While a huge asset to any memory service, many patients can be readily assessed and a diagnostic formulation established without referral to neuropsychology, access to which may be quite limited. Such patients encompass those with moderate deficits where the underlying process is clear, as well as those 'worried well' who have mild attentional symptoms without any evidence of any objective deficits. Similarly, patients with advanced dementia with global impairments will not benefit from detailed neuropsychometry. The discriminative value of neuropsychology lies in the assessment of those patients with early, mild symptoms and deficits and/or those whose results on cognitive assessment scales fall in the

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equivocal range. Neuropsychological assessment is also useful at teasing out affective contributions to cognitive symptomatology. More rarely, it is useful in identifying psychogenic amnesia, or factitious cognitive disorders where themes such as effortful underperformance and approximate answering emerge.

The involvement of an occupational therapist (OT) is often also required for a robust and comprehensive cognitive assessment. In particular, the OT can perform practical and measurable assessments of functional capacity. This can be particularly useful in the domiciliary setting where the environmental and/or social contexts can be observed. Such assessments are especially valuable where there is a mismatch between patient and informant accounts of functional performance or where it is suspected that caregivers are compensating for a patient's deficits.

General neurological examination

As cognitive symptoms in neurodegenerative disease are reflective primarily of incipient or established focal atrophy, it stands to sense that other neurological signs may coexist with cognitive abnormalities. As such, a careful and detailed neurological examination is always warranted in the patient presenting with cognitive decline. Observation of the patient during the consultation, from the moment they are called from the waiting room, can yield much information long before one has recourse to the formalized neurological examination. The 'head turning sign', whereby the patient turns to the caregiver for assistance in providing the history, is a sensitive marker of cognitive impairment (Larner, 2012) and it may be more predictive of AD and aMCI than other syndromes (Fukui et al., 2011). Movement disorders—hypo- or hyperkinetic—will be readily apparent. Parkinsonism is the pre-eminent hypokinetic movement disorder and is defined by the presence of two or more of rigidity, bradykinesia, tremor, and postural instability; the latter three features can be identified by observation alone. Hyperkinetic movement disorders, such as chorea, are also easily discernible; it is worth noting that up to 11% of patients with Huntington's disease present after the age of 60 and that cognitive impairment, rather than the movement disorder, may be the greater source of disability in this group (Chaganti et al., 2017) prompting referral to a memory clinic before a movement specialist. Myoclonus (brief, simple, irregular muscle jerks) in the setting of cognitive decline suggests a broad differential; in the context of rapidly progressive dementia, it raises the spectre of prion disease (peak age of onset 65–74 years) (Puoti et al., 2012); more commonly, it is seen in AD and the atypical parkinsonian disorders, particularly DLB and corticobasal syndrome (Kiziltan et al., 2017).

The formal neurological examination should then be completed. Important cranial nerve abnormalities, not to miss, include visual field deficits, eye movement abnormalities, hypomimia, dysarthria, and/or other bulbar or pseudobulbar signs (e.g. a weak, fasciculating tongue or a spastic, atrophic tongue with strangled speech and a hyperactive gag

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reflex). Listen carefully to the content of speech, but also to its volume (for hypophonia of parkinsonism) and intelligibility and for the phenomenon of tachyphaemia seen in extrapyramidal disorders (rapid, 'festinant', and often poorly decipherable speech). Frontalis overactivity is highly characteristic of PSP. A brisk jaw jerk is an upper motor neuron sign characteristic of, but not exclusive to, MND.

Muscles should be inspected for atrophy or fasciculations. Tone should be tested in the limbs, and rigidity or spasticity noted. Paratonia ('Gegenhalten') can be more difficult for the non-specialist to confidently distinguish but refers to a progressive increase in tone with manipulation of the limb by the examiner—this is frequently seen in dementia patients. Pyramidal weakness or other long tract signs, such as ankle clonus, hyper-reflexia, or extensor plantars, may be of relevance to the diagnostic formulation; such upper motor neuron signs are indicative of corticospinal tract dysfunction, pointing to vascular disease or possibly an anterior horn cell process such as MND. Patients should be assessed for bradykinesia (a decrement in amplitude with repetition of finger taps or other rapid alternating movements of the limbs). Appendicular and midline coordination should be tested by finger-nose, heel-shin, and heel-toe gait testing. Detailed sensory testing is probably unnecessary in many patients, but it is important to assess the general integrity of sensory function and to ensure there is an absence of sensory inattention in those with symptoms suggestive of apraxia, as unrecognized sensory deficits could lead to an inaccurate label of apraxia.

Frontal release signs, such as the grasp reflex, pout reflex, and palmomental reflex, are indicative of loss of frontal inhibition of primitive reflexes present from infancy. The grasp reflex is definitely present when the patient is clearly instructed by the examiner not to take the examiner's hand and/or to release it. The palmomental reflex may be less specific for neurodegenerative disease, with a prevalence of up to 25% in normal older adults (Jacobs and Gossman, 1980).

Dominant parietal function can be assessed by asking the patient to identify their right and left hands, as well as by tests of visual and sensory inattention. Cortical sensory signs, such as dysgrapaesthesia (inability to identify a simple digit traced on the palm), astereognosis (inability to identify an object placed in the palm without a visual cue), and poor spatial two-point sensory discrimination, are evident in many patients with parietal dysfunction. Tests for apraxia include requests to mimic hand/finger movements or to mimic gestures or activities such as washing teeth with an imaginary toothbrush, brushing one's hair, saluting a senior in the army, or demonstrating the gesture used for hitch-hiking.

Gait should be observed for stride length, base, foot clearance, arm swing, and turning performance. Parkinsonian gait and the 'magnetic' gait of normal pressure hydrocephalus and other movement disorders are thus identified. In contrast to when upright and weight-bearing, patients

with apraxia of gait can mimic bicycling movements when supine or trace a number on the floor with the feet while seated.

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Physical assessment

Chapter: Physical assessment

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Philosophy and approach

Physical health problems in older people are manifold and various. They may be acute or long term; of different degrees of seriousness; with or without functional consequences; and may or not impact on others. They will be managed in different settings: at home, a primary care facility, a care home, as a hospital in-patient, out-patient, or in a day hospital, in an alternative community setting such as intermediate care, or at dentists', opticians', or audiologists' premises. The purposes and methods of assessment vary; there are common themes, but some are situation-specific.

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An older person with mental health (MH) problems requires physical assessment:

- To identify physical signs that support a psychiatric diagnosis, e.g. neurological features of dementia with Lewy bodies (DLB), vascular dementia, or Huntington's disease.
- The MH problem may be caused by a physical disorder, e.g. anxiety in thyrotoxicosis; adjustment disorder or depression in chronic pain, physical disability, or after a stroke; Korsakoff's psychosis.
- The MH condition may have physical consequences, e.g. weight loss, malnutrition, or inability to undertake activities of daily living (ADL).
- The MH condition may mimic a physical disorder, e.g. somatization, hypochondriasis.
- Physical and mental disorders may have shared features, e.g. fatigue, communication impairment, anorexia, constipation.
- Physical and mental conditions frequently co-exist, and their functional consequences add up or interact (Prince et al., 2007; Fox et al., 2014; Bunn et al., 2014).

Many aspects of both physiology and disease are alike, regardless of age. However, older people have some characteristic differences (Evans, 1990):

- Multiple pathologies are common, or almost universal (Barnett, 2012).
- Presentations of disease can be non-specific, atypical, or functional (e.g. falls, delirium, immobility, incontinence, 'not coping').
- Older people are more prone to complications, both of diseases and their treatments.
- The health of older people may deteriorate rapidly, reflecting frailty and loss of homeostatic reserve.
- Explicit rehabilitation is often required to restore function after illness or injury, and older people are vulnerable to deconditioning (loss of muscle mass, strength, and functional capacity) after a period of inactivity or bedrest.
- Their functional ability is more dependent on the physical and social environment.
- The end of life may be approaching.

Older people vary one from another in their health, abilities, behaviours, resources, and social arrangements more than younger people, so doctors must be flexible in their approach. Some older people are fit and active, and need the same approach to investigation and treatment as younger people. Others have a complex mixture of multiple acute and chronic medical, mental, and social disorders, and there may be multiple stakeholders as well as the patient (including relatives, carers, and

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services such as care homes). The social dimension is especially important, as older people are both dependent on, and vulnerable to loss of, human relationships and care arrangements. The geriatric medical approach to addressing these problems has developed into the framework of the Comprehensive Geriatric Assessment (CGA), which has five dimensions:

1. Medical (acute and chronic, including polypharmacy, adverse drug effects, and medicines management).
2. Functional (ADL, behaviour, safety).
3. MH (mental illness, cognitive disorders and psychological impact of disease).
4. Social (relationships, human support).
5. Environmental (accommodation, and adaptations to enable independence).

MH practitioners may recognize this as the biopsychosocial model. Assessment of these domains enables development of a multiprofessional management plan. The approach is demonstrated to maintain health and function, reducing mortality and the need for long-term institutional care (Stuck et al., 1993, Ellis et al., 2017). In the context of vulnerability, intercurrent illness, and progressive disease, the assessment and management plan are rarely static, but ever-changing—a continuous process, rather than a single event.

The ‘medical model’, based on diagnosis and specific curative medical treatment, is important, but in itself insufficient. Prevention, palliation, the giving of information, counselling or teaching, negotiation of goals, multi-disciplinary management, restoration of function, adapting the physical and social environment, and support for families and other carers are all equally important. The healthcare of older people draws on a variety of models or frameworks, depending on the problem and goals of treatment (Table 11.1).

Table 11.1 Models of healthcare for older people.

Model	Approach
Prevention	Anticipatory treatment to avoid ill health in high-risk groups
Medical	Diagnose, treat
Rehabilitation	Cycle of problem identification, analysis, multi-professional therapeutic intervention and reassessment, directed at maximizing physical and social functioning

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Palliative	Meticulous management of symptoms, open communication, attention to psychological, social and spiritual aspects, advance care planning
Person-centred care	Value and respect for personhood, individualized care, empathic understanding, communication and relationships to promote wellbeing and reduce distress
Recovery model	Emphasize hope, identify positive attributes and abilities, set achievable goals, take risks, accept failure
Social model	Environment and relationships adapted to individual's differing abilities

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Frailty and crises

Frailty is defined as vulnerability to deterioration in the face of a stressor (Clegg et al., 2013). The stressor may be accident or injury, acute illness, iatrogenic (e.g. an operation or drug side-effect), psychological, social, or environmental (e.g. moving house, admission to hospital).

Recent research has attempted to define frailty among older people based on generic features. Many people with chronic ill health, including diabetes, chronic obstructive pulmonary disease, sensory impairment, severe mental illness, intellectual disabilities, or dementia are vulnerable, and they may or may not be frail in the sense applied to older people. Some diagnoses overlap or are closely related to frailty, for example, features of depression may be difficult to distinguish from frailty (Vaughan et al., 2015). Three models of frailty measurement have emerged:

1. The 'frailty phenotype': based on five risk factors for adverse events or death identified in an epidemiological study (unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed, and weak grip strength). Three or more being present defines frailty, one or two present defines 'pre-frailty' (Fried et al., 2001).
2. The 'cumulative deficits' model: uses a checklist of problems to derive a frailty index (FI, the proportion of problems present) (Mitnitski et al., 2001). The approach can be applied to any data set, giving comparable results; for example, the electronic frailty index (eFI) derived from routinely available UK general practice data

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(Clegg et al., 2016), or a simple practical operationalization, the Edmonton Frail Scale (Rolfson et al., 2006).

3. The Clinical Frailty Scale: a nine-point, ordinal, vignette-based scale based on medical problems and disability, which closely correlates to the cumulative deficits FI (Fig. 11.1) (Rockwood et al., 2005; Dalhousie University, 2018).

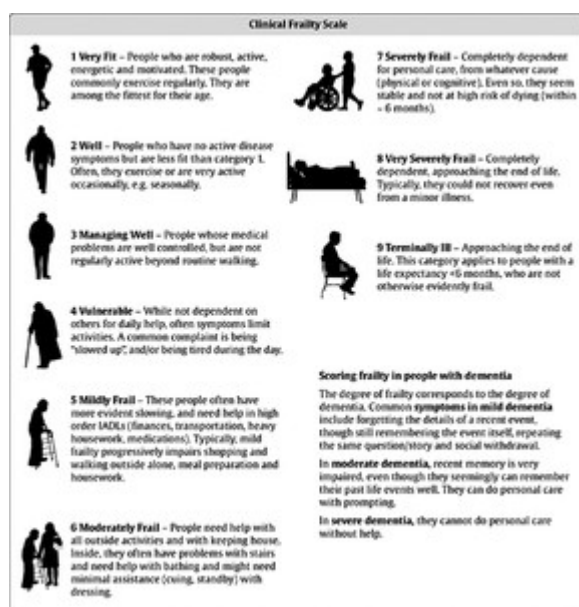


Fig. 11.1
The clinical frailty scale.

Reproduced with permission from Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005 Aug 30;173(5):489–95.

Frailty scores, such as the Edmonton Frail Scale or the Clinical Frailty Scale, have been applied to older surgical patients (to identify those requiring prospective CGA pre- and post-operatively), in emergency departments and 'acute frailty units' to identify patients requiring early multi-disciplinary assessment, and in general practice to identify people at high risk of hospital admission for pro-active case management or end-of-life care.

A crisis is a time of difficulty, risk, or danger, or a time when important decisions must be made. Crises characterize frail older people and result in disruption, distress, and risk of death, complication, or permanent functional loss. Crises may be due to acute physical illness or injury (especially resulting from falls); functional decline (dehydration, immobility, or incontinence); MH problems (delirium, psychosis, poor safety awareness), social or environmental disruption (e.g. death or illness of a spouse, absence of a family member or carer, holidays, hospital admission), or failure of care systems (e.g. home care being

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unavailable or a care home being understaffed). Much preventative, elective, and social care aims at avoiding crises.

Assessment of a crisis aims to describe and understand it ('history of presenting complaint'). It will often be unclear what the relative contribution of physical, mental, and social factors are at the point of crisis, in the context of multimorbidity, and non-specific presentation of disease. This often results in acute hospital admission, where the task is to identify or exclude physical illness, maintain or restore function, and make plans (including for non-hospital alternative care, or end-of-life care). MH crises in older people often present in this way, emphasizing the importance of well-integrated liaison MH services in acute hospitals (and, conversely, for MH teams to have confidence in recognizing and assessing physical health problems in both community and acute psychiatric settings).

Information gathering

Assessment of a complex older patient takes time. There is no avoiding this, although some tasks can be delegated or distributed among a multi-disciplinary team. An unwell older person may not have the stamina to continue a long history and examination session in one go. It may be necessary to do no more than is immediately necessary and come back later (a 'rolling' consultation). Knowledge of prior medical problems and experience can be invaluable.

The history is central to medical assessment. Assessment at the point of presentation or admission to acute services is unlikely to be comprehensive, and the nature of the problems may emerge or evolve over time. 'Information gathering' is a more prolonged process than 'history-taking' and may extend over several days or weeks. Further information is gained from:

- third-party, 'informant', or 'collateral' interview (including to establish a diagnosis, ascertain problems, and determine baseline function, e.g. in cognitive impairment or in severe mental illness, to assess falls or loss of consciousness, ascertain social and environmental resources, expectations, and care planning information);
- observation, for change or fluctuation (e.g. in delirium);
- assessment of wellbeing, behaviour, and function, which will likely involve families, nurses, and therapists. Multi-disciplinary working and communication is important.

Presenting symptoms

Physical symptoms may be 'typical', such as weight loss, pain, breathlessness, or disturbance of consciousness, or 'non-specific'. The classical non-specific presentations of disease in older people, or the so-

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called 'geriatric giants' (immobility, falls, confusion, incontinence, 'not coping') (Isaacs, 1992), are 'non-specific' because they can be caused by many different pathologies. Non-specificity can be overemphasized, however; most presenting symptoms in medicine are not specific to a single pathology. Breathlessness, for example, may be caused by cardiac, respiratory, metabolic, and psychogenic problems; or weight loss may be malignant, gastrointestinal, metabolic, or psychiatric.

The non-specificity of the presenting complaint should be explored by questioning about more 'typical' symptoms. Experienced doctors use 'inductive thinking' in making assessments of frail older people. The doctor 'tests' hypotheses about what the problem might be, using questioning, examination, or investigation. This requires knowledge of diagnostic possibilities, judged by the presenting complaint, symptoms, and prior history, or simply experience and suspicion. These hypotheses are tested by asking questions to try to rule things in or rule them out. The alternative is a 'checklist' approach to history-taking, seeking the presence or absence of multiple different symptoms, which is lengthy and inefficient. The repeated questioning involved may overwhelm someone with cognitive impairment or a mood disorder, or fatigue someone who is frail.

A key part of the history is to establish the time-course, which is often longer than is usual for most 'acute' medical problems, playing out over months or years. Change in ability is often as important as onset of a new problem, since chronic disease and disability are common. We may need to establish a 'baseline' ('do you usually have any problems with your health?'; 'what can you do when you are at your best?'). This can be conveniently specified in terms of level of function ('can you walk?'; 'do you get out of the house?'; 'who does the shopping?'; 'who pays the bills?'). Then establish if problems started suddenly, or if gradually, over how long, and if they had occurred before.

Problems with history-taking

History-taking can be difficult because of:

- Cognitive impairment
- Deafness
- Aphasia
- Language (older non-native English-speakers may never have learned English, or may have lost the ability with stroke or dementia)
- Anxiety, depression, or delusions
- Tiredness, lack of concentration, or loss of stamina.

For people living with dementia, forgetfulness is a problem, but other aspects are also important, such as problems with insight, abstract thinking, and the perception of changes over time. However, people living with dementia can often report accurately about symptoms that they are

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currently experiencing, although communication impairment may make this difficult. It is important to try to involve the person in describing what is wrong, even when you suspect that the information is unreliable. This is courteous, inclusive, and respects identity and 'personhood'—a 'patient-centred' approach. However, if the person cannot give a good account of their problems, do a mental state and physical examination, and seek your history elsewhere (from an informant, using the telephone if necessary). In the case of delirium, cognition and attention fluctuate, and history-taking may be easier if attempted again a few hours later.

Hearing problems, usually due to presbycusis or wax, are present in 60% at age 70–80, and 90% of those over 80. Take the opportunity to make a referral to audiology services for hearing assessment and management if indicated. Make sure hearing aids are in place, switched on, have working batteries (which last less than a week when in constant use) and are not blocked with wax. Find a quiet room to speak in or minimize background noise (turn off the radio or television). Talk a little louder and more slowly than usual, but do not shout. Let the person see your lips as you speak. Gesture can help. Writing questions down is very laborious.

Aphasia is a disorder of language, common after stroke and often in dementia (although less well-recognized in this condition). Receptive aphasia is inability to understand (spoken and usually written) language. Expressive aphasia is the inability to speak (or write). Both come in degrees of severity. Speak as if speaking to a competent but not fluent, non-first-language English-speaker. Keep it simple: avoid jargon or complicated words. Use short sentences. Avoid double negatives. Repeat if necessary, and use gesture, pictures, and writing. The patient or relatives may be able to help tell you what works best. A joint session with a speech therapist may also help.

Various people can help translate for non-English speakers. Relatives are often available, able, and willing. Many hospitals keep registers of staff who speak other languages, and who can help. A professional interpreter may be more difficult to arrange, but sometimes may be necessary, as they may be able to 'advocate' as well as 'translate'. A three-way telephone conference call with a translator can be arranged if the patient does not find the whole experience too bewildering.

The rest of the medical history

Past medical history obtained from the patient, general practitioner, or the medical records may be extensive. It is worth questioning labels. Who diagnosed dementia, ischaemic heart disease, epilepsy, or Parkinson's disease? What were the symptoms? Is the diagnosis still valid? Is the diagnosis still active? Diagnoses are not always accurate, but you need good reasons to contradict a specialist opinion.

Always quantify the impacts or effects of diagnoses. If there is arthritis, specify the joints affected. A stroke patient may have fully recovered,

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been rehabilitated to reasonable function without full recovery, or been left wholly dependent on others. The label alone is of little value. Heart failure, angina, claudication, respiratory disease, or arthritis can be quantified in terms of exercise tolerance or walking distance, including some formal scales e.g. the New York Heart Association heart failure classification (The Criteria Committee of the New York Heart Association, 1994), or Medical Research Council breathlessness scale (Fletcher et al., 1959).

‘General enquiry’ can be useful, but has to be brief, and may have a different slant than in younger people. Ask about dizziness, falls, constipation, bladder symptoms, eyesight, hearing, teeth, feet, appetite, and weight loss. It may be that you can be proactive in using the opportunity of an older person presenting to your services to address physical health problems that impact on their quality of life, but which otherwise may be neglected.

Drug history

Drug history and arrangements for medicines management are very important. Older people, on average, take more prescribed drugs than younger people and are more prone to adverse effects. About one in eight hospital admissions is caused or contributed to by a drug adverse effect (Duerden et al., 2013). Look out for and question the need for common culprits (Tables 11.2 and 11.3). Multimorbidity is an important driver behind polypharmacy, which may therefore be both appropriate and unavoidable. The ‘single-disease approach’—treating medical conditions in isolation—increases the risk of potentially inappropriate medication (Salisbury, 2012).

Table 11.2 Adverse effects of drugs, by drug type.

Drug	Common adverse effect
Antibiotics	Diarrhoea (including <i>Clostridium difficile</i>), rash, nausea, abnormal liver function
Anticholinergic drugs	Delirium, cognitive impairment, dry mouth, urinary retention, blurred vision, dyspepsia, constipation
Antidepressants	Falls, nausea, hyponatraemia, extrapyramidal (SSRI*), anticholinergic (tricyclics, paroxetine), drowsiness, mania

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Anti-epileptic drugs	Drowsiness, cognitive slowing or impairment, ataxia, paranoia, abnormal liver function, osteomalacia
Antiparkinsonian	Delirium, hypotension, dyskinesia, nausea
Antipsychotics	Drowsiness, extrapyramidal effects (including atypical antipsychotics), falls, impotence, anticholinergic effects
Benzodiazepines	Drowsiness, falls, cognitive slowing or impairment, withdrawal effects, paradoxical agitation
Cardiovascular (antihypertensives, anti-anginals, anti-arrhythmics)	Hypotension (especially postural), falls, heart failure, metabolic, delirium
Diuretics	Lower urinary tract symptoms, dehydration, hyponatraemia, hypokalaemia, hyperglycaemia, gout, hypotension
Laxatives	Diarrhoea, faecal urgency, faecal incontinence
Lithium	Polyuria, tremor
Non-steroidal anti-inflammatory drugs (NSAIDs)	Gastritis, peptic ulceration, renal failure, fluid retention
Opiates	Constipation, nausea, hallucinations, delirium, drowsiness, itch
Corticosteroids	Weight gain, thin skin, diabetes, osteoporosis, myopathy, psychosis (high dose)

*SSRI: selective serotonin re-uptake inhibitor

Table 11.3 Adverse effects of drugs, by adverse effect.

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Adverse effect	Possible culprit drug
Anorexia, nausea	Opiates, metformin, antibiotics, anticholinergics
Constipation	Opiates, anticholinergics, verapamil
Delirium	Anticholinergics (including tricyclic antidepressant, antiparkinsonian, surgical premedication, bladder instability drugs), opiates, drug withdrawal
Diarrhoea	Laxatives, antibiotics, metformin, proton pump inhibitors, NSAIDs*
Falls	Sedative and antidepressant drugs (TCA** and SSRI***), hypnotics, drugs causing hypotension
Hypotension	Diuretics, all cardiovascular drugs except digoxin, levodopa, antipsychotics
Oedema	Calcium channel blockers, beta blockers, fludrocortisone, NSAIDs*
Rash, pruritus, abnormal liver function	Any

*NSAIDs non-steroidal anti-inflammatory drugs;

**TCA tricyclic antidepressant;

***SSRI selective serotonin re-uptake inhibitor

People living with frailty or dementia are especially vulnerable to drug adverse effects; close attention to all aspects of clinical therapeutics is required. Ask about the indication, from the patient or carer, electronic care records (including the electronic Summary Care Record in the UK), or general practitioner (GP). For example, furosemide is often prescribed for ankle swelling. In the absence of overt signs of heart failure, no more than half of patients actually need it (ankle swelling may also be caused by dependency, immobility, hypoalbuminaemia, or venous/lymphatic obstruction).

Question whether drugs have been assessed for effectiveness—especially antidepressants, cholinesterase inhibitors, antipsychotics, and

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antiparkinsonian drugs. It is easy to commence a trial, and never follow it up, or fail to withdraw the drug if there has been no clear benefit. If there is good evidence of benefit, the drug should be continued. If not, consider or suggest a trial of stopping it. Dose minimization may be possible (e.g. can furosemide be reduced to 20mg/d in stable heart failure?).

'Tablet burden' is a real issue for an older person on 10 or more different drugs. Distinguish between preventative drugs (e.g. vascular: antithrombotics, cholesterol and blood pressure lowering; bone health: calcium and vitamin D, bisphosphonates), and those controlling active problems (e.g. anti-epileptic drugs, anti-arrhythmics, diabetic drugs, analgesics, anti-anginals, heart failure, and bronchodilators). If a preventative drug is causing problems, it should be stopped. The odds on a preventative drug doing good are usually too slim to justify side-effects ('numbers needed to treat' to prevent a single event are usually in the tens or hundreds). In very frail patients, or those at the end of life, drugs should be limited to those that are directly relieving symptoms or improving function.

Ask about medicines management and compliance. Patients may openly admit they do not take all of their tablets. Who supervises the taking of drugs, and whether compliance aids are used (e.g. a dosette box or blister pack)? Difficulties in swallowing medications may be easy to address with the help of a pharmacist, who can suggest alternative formulation or routes (liquids, transdermal preparations). Child-resistant containers are difficult to open and usually inappropriate.

Ask about allergies and previous adverse effects, specifying the exact reaction if possible. Calls to GPs and reviews of records may be needed to clarify. Many adverse effects get called 'allergies'—few actually are, but you will still need to know about them. If an expected drug is missing (e.g. a statin in vascular disease, ACE inhibitor in heart failure) efforts should be made to find out if there is a reason.

Social and functional history: activities of daily living (ADL)

These aspects cover two or three dimensions of CGA, but are interrelated and often collected together. They form the core of an occupational therapy assessment, but doctors should know about them, too. For many older people they are key to understanding problems and possible solutions.

A problem with function (a 'disability'), e.g. walking or safety awareness, may be the presenting problem. Function is the final common pathway for the effects of many different diseases, or combinations of diseases. Problems with walking may be due to pain, weakness, breathlessness, falling, vision, dementia, depression, or fear. In assessment, we may start with the disability and work 'backwards' to identify the signs and symptoms (impairments) that are associated with it, and from that, work out the underlying diagnoses. Function gives insight into cognition,

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confidence, physical ability, and available support networks. Deterioration in function can be an important indicator of a deterioration or relapse in MH. Usually it is problems with function that make independent living or discharge home from hospital difficult, and may necessitate professional domestic or personal care support, so assessing function is part of care and discharge planning. Documented function provides a baseline against which to assess subsequent changes in health. Quantifying function tells us about disease severity. Collateral history to corroborate the patient's account is often important.

The range of activities that might be considered is wide. As a minimum, ask about eating and drinking, mobility, continence, and behaviour. An otherwise fit older person might be asked about driving, shopping, cooking, and money management. Stair climbing, walking outdoors, walking indoors, dressing, getting to the toilet, wheelchair use, and bed to chair transfers can all be considered. If problems are identified, ask how they are overcome (who shops for food? how do you get to the toilet?). Falls are common—ask specifically—as is incontinence and other lower urinary tract symptoms (LUTS), e.g. urgency, pain, or dribbling. This may not be volunteered—develop a form of words that is not open to offence, but don't be embarrassed yourself ('Do you have problems with your bladder? Do you always get to the toilet on time?'). There are many ADL scales that can standardize and quantify assessment, including the Barthel Index, Bristol ADL scale, Disability Assessment in Dementia, and Amsterdam ADL scale.

'How do you occupy your time?' can be a revealing question, and give clues about abilities, social networks, priorities, and resources. Successfully completing the *Times* crossword is a good index of cognitive competence. Many people do little more than watch television: ask what programmes they watch—are they able to follow soap operas and series? Can they answer the questions on quiz shows?

What someone does day to day depends both on their capacity to do tasks and the physical and social environment in which they do them. It also depends on opportunity, restriction (e.g. family concerns about safety, risk, or falls), and the use of aids and appliances. In assessing function, you must also assess the environment and levels of help available and used. Do they live with someone? If so, who? What sort of accommodation do they have (house with stairs, ground-floor flat, care home)? Do they have help from family, or paid carers? Make sure also to ask after the health of an elderly spouse or co-resident.

Functional improvement will often be the metric by which the success of a treatment, progress towards a goal, or by which treatment failure, recurrence, complications, or the approach of the end of life are judged.

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Third-party history

Most older people are able to give a full account of themselves and their symptoms. If the person has mental capacity, it is technically a breach of confidentiality to involve anyone else without their permission. It is always courteous to ask permission to consult others, although in many cases the consent will be implicit, and need not be explicit. If someone cannot give an account of themselves, best practice, best interests, and (in the UK) the law requires that others be consulted. The opportunity to explain problems or educate key carers in a joint consultation can be invaluable.

Information from an informant is usually required in cases of cognitive impairment, aphasia, or other communication difficulties, non-specific 'not coping', loss of consciousness, and falls. Thirty per cent of people experiencing syncope have no recall of losing consciousness; epilepsy is a diagnosis made primarily on third-party history; the deathly pallor of cardiovascular syncope or presyncope can be a helpful diagnostic pointer.

Retake the history from the informant, ascertain the baseline level of health and function, and the nature and time-course of decline. Identify and characterize prior ADL, as in the 'functional history', and current problems. Also find out about cognition, especially time-course of deterioration, severity, and impact on behaviour. This may be done together with or separately from the patient, by telephone if necessary. Carers may wish to ensure that you fully understand what they are experiencing, especially where there is fluctuation, and this may include information upsetting to the patient.

Family members or others with caring responsibilities often bear physical and psychological consequences—so-called carer strain—which can result in inadequate care or breakdown in care. This should be ascertained if appropriate.

There can be a tendency for a carer to want to advocate for or speak over a person with cognitive or communication problems; we must guard against failure to listen to the patient's opinions. Inclusion is important, and the impression that information is being passed on 'behind the back' of the patient must be avoided.

Others may also have useful information. Consider phoning the general practitioner, or social care providers (home care, or wardens of assisted living facilities). Look out for visitors like neighbours who may have been providing substantial help but who are not recorded in medical or nursing records. Professionals working in care homes or the community can help by ensuring that key items of health, personal, and social information are available during episodes of emergency or respite care. Hospitals can reciprocate on discharge.

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Anticipating hospital discharge

In hospitals, 'discharge planning begins on day one' is a slogan that may or may not be applicable in complex cases (NB: the answer will often be 'it depends'). It is important to keep options open (such as returning back home) before a full assessment and decision-making process has been undertaken.

When completing admission paperwork (including emergency MH admissions), make life as easy as possible for colleagues who look after the patient later by recording basic aspects of social and functional history, and sources of support, especially if there is a relative present who may not be available later. If strong opinions about the future are expressed early on ('she's not coming home'), record them, but try to keep all options open for as long as possible.

Discharge home with support isn't always possible, but is usually preferable, and quicker, than care home placement. Moreover, it may be that, despite severe disability and dependency, someone already well supported at home can be discharged quickly after resolution of a minor crisis even when you would have anticipated a long and difficult admission. However, only follow this route if you know the support arrangements that are in place.

End-of-life planning

Sometimes you need to identify quickly that terminal care is appropriate, and plan accordingly. This may include information about advance decisions to refuse treatment, prior discussions or decisions, priorities, preferences, fears and values, attitudes to risk, and available informal support and professional care. End-of-life planning will include ascertaining problems and distressing symptoms, identifying who should be involved in discussions, and consideration of spiritual needs.

Physical examination

The procedure for examining each physical system is no different from those used in any other adult. Often this will be targeted at the particular problem being addressed, but at least once during a hospital admission, someone should do a full physical examination. It is important to ensure that this is followed up on if it was not possible at the point of admission. We must pay careful attention that all parts of the physical examination are performed.

General appearance

An acutely ill patient is often disengaged, lethargic, and may be drowsy; these features may represent a hypoactive delirium. Weight loss, cachexia, or loss of muscle mass may indicate severe illness such as cancer, malnutrition, long-standing inactivity, chronic disease including dementia, or a treatable condition such as thyrotoxicosis or tuberculosis.

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Unkempt appearance may be a warning sign, indicating impairment of function.

A patient prone to agitation, restiveness, or described as noncooperative should be approached carefully. Establish a rapport by introducing yourself and friendly small talk. Try to avoid anything that might be interpreted as a threat. Do not rush. Hand holding and smiling may help. Talk calmly and in a friendly tone, and explain everything that you are doing before and as you do it, so-called 'talking-through', as you examine or perform a procedure, to try to reduce fear. Adopt a nonthreatening body posture (sitting or squatting), but ensure your personal safety. Prioritize what is most important to examine. If the person objects or resists, and cannot be persuaded otherwise, do not persist. Use observation, examine what you can, document your attempt, and come back another time if necessary ('leave and return' strategy).

Communication

Assessing communication is part of both neurological and mental state examinations, but many physicians neglect to examine or describe it formally. Interpreting the history, mental state, distress, insight, mental capacity, and engagement with and adherence to treatment all depend on communication.

Initial assessment is informal and occurs during conversation. Sensory impairment (deafness, visual impairment) should be noted and mitigated as much as possible, and a translator sought if needed. Dysphonia is a disorder of voice production ('hoarse' or whispery), which implies vocal cord paralysis or pathology. Dysarthria leads to problems with word production, and may be due to face or tongue weakness, or incoordination ('cerebellar-type' dysarthria). Aphasia is inability to understand (receptive) or express. Understanding can be tested by asking the person to follow motor commands, initially simple ('close your eyes') but also more difficult (three-stage or complex instructions such as during neurological examination). Word-finding difficulties may be evident in spontaneous speech, and can be tested through object naming or picture description. Other tests include sequences (days of the week), multiple choice or yes/no answers, and listening for crying, swear words, or unformed sounds.

Communication may be affected by physical health (pain or breathlessness), other aspects of cognition (memory, reasoning, or insight), mood, thought content (delusions), intelligence, and world view.

Postural blood pressure

Blood pressure varies with circumstances, and in older people may vary dramatically throughout the day, especially in people with delirium and dementia. Drugs or autonomic failure make postural hypotension quite common (25% of those over 65 years). When investigating dizziness or falls, measure blood pressure after five minutes lying, then after 40

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seconds, one minute, and three minutes standing (an automated sphygmomanometer takes about 20 seconds to make a reading). Record if the patient felt dizzy or lightheaded on standing, and if the pulse rate increases (as it should). A systolic drop of 20mmHg, or diastolic drop of 10mmHg is significant. Blood pressure falls that have not reversed within 40 seconds of standing are associated with increased risk of falls (Bhangu et al., 2017).

Mouth and dentition

Oral health is an important consideration, and is of increasing relevance with a greater proportion of people retaining their natural teeth into old age. Poor dentition can cause dysarthria and swallowing difficulties, as well as being a risk for infective endocarditis. Dental pain or abscess may be a source of distress in someone who cannot communicate. Be very careful to prevent dentures getting lost, especially in hospital.

Vision

Distinguish between uniocular loss (a problem anterior to the optic chiasm, broadly ophthalmology) and homonymous loss (a problem posterior to optic chiasm, broadly neurology). Sudden vision loss is an emergency that requires immediate explanation (do fundoscopy, and/or refer to an eye emergency department). Ensure that an adequate explanation has been reached for any visual loss; refer on to ophthalmology if this is not clear, although optometrists and orthoptists can also examine the eye. Any sudden change in function might represent sudden visual (or hearing) loss in someone who cannot communicate well.

Musculoskeletal system

Joint disease is very common in older people (50% of 80-year-olds have knee arthritis), and may contribute to immobility, falls, dizziness, and pain. Examination requires observation, testing range of movement in all directions, and during function, noting pain and deformity. Examine the shoulders and hands if symptoms dictate. Look at the knees and hips, and the bulk of quadriceps muscles. Record if the knees can be fully extended (they should go into a few degrees of hyperextension), and the extent of any fixed flexion deformity. Test flexion/extension and internal/external rotation of the hips. If painful, think about the shortened externally rotated leg in hip fracture. An apparently painful hip, with a normal X-ray, may be due to a pelvic fracture. Joint pain may be referred from the joints above or below. Small joint arthritis of the hands and feet may be distressing and disabling. Neck arthritis may be associated with dizziness on standing when the neck is extended (due to disordered proprioception, not vertebrobasilar ischaemia). Kyphosis indicates vertebral shape changes due to osteoporosis. A vertebral compression fracture or a rib fracture produces pain and severe localized tenderness.

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Feet

The feet should always be examined, especially in people with diabetes. Look for ulcers, deformities, signs of ischaemia, sensory loss (e.g. neuropathy in diabetes), and neglected nails (onychogryphosis).

Neurological examination

Many doctors consider this the most difficult part of physical examination, and thus do a brief version of little value, neglect it entirely, or say that examination was impossible. Mental illnesses are (usually) diseases of the brain, so neurological examination is as important for the psychiatrist as the geriatrician.

Examining the nervous system can be lengthy, which is both time-consuming and often beyond the stamina of a frail or ill patient. Musculoskeletal problems may make neurological function difficult to interpret. Skilled observation alone can provide many clues, e.g. a patient walking into a consultation displays involuntary movements, cannot follow what you are asking, or is agitated or uncooperative. Examining the nervous system properly takes practice, and some signs are subtle (such as fasciculation, bradykinesia, or incoordination).

The key is to be clear about the purpose of the exam. The 'nervous system' is a collection of several systems: higher thought and consciousness, vision, brain stem, hearing and balance, speech, pyramidal motor, extrapyramidal motor, coordination, sensory, and autonomic. An old adage states that the purpose of neurological examination is to ask: '*where* is the lesion?' followed by '*what* is the lesion?' (i.e. what pathologies might occur at that location?), to which we might add '*so what about* the lesion?' (i.e. what are the functional consequences?). We use knowledge of neuroanatomy to determine where the lesion is. Where we look is determined by the nature of the problem and the symptoms revealed in the history. If we are investigating falls, we need to examine vision, vestibular, and pyramidal function, coordination, feet tactile sensation, and proprioception. If the person has cognitive impairment, we are interested in alertness and attention, extrapyramidal or parkinsonian symptoms (bradykinesia, increased tone, tremor, postural instability), or pyramidal motor symptoms (weakness, increased tone, hyperreflexia, up-going plantar response).

If you expect the examination to be normal, in the absence of specific neurological symptoms, or 'red flag' features (focal onset epilepsy, or indicators of raised intracranial pressure, e.g. headache, vomiting, drowsiness) a minimum examination should reassure you that a structural brain lesion is unlikely (Donaghy, 2005). It takes about five minutes to perform and comprises: gross visual acuity and visual fields; eye, face, palate, and tongue movements; speech; arm tone; pronator drift (ask the patient to hold their arms out in front with their eyes closed, as if holding up a parcel, for 20 seconds), power in shoulder abduction and first dorsal interosseous (index finger abduction); finger-nose coordination,

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dysdiadochokinesis; hand and foot sensation; and standing balance/Romberg's test and gait.

If cooperation is lacking, observe and use ingenuity. You may be able to detect spatial inattention and visual field loss, facial asymmetry, speech and swallowing problems, abnormal limb movements, symmetry of limb movement and co-ordination, ability to stand from sitting, gait, and possibly limb tone, and hand grip (via a hand shake).

Be aware that physiotherapists also perform a sophisticated neurological examination, albeit subtly different from that done by doctors. It is functionally (rather than diagnostically) orientated, and includes items unfamiliar to doctors, e.g. muscle activation in standing. Speech and language therapists examine the lower cranial nerves as part of swallowing assessment as well as communication. Occupational therapists work through 'activity analysis', which is based on neuropsychological understanding, including assessment of spatial neglect, apraxia, sequencing, or executive function problems.

Nowadays, access to CT or MRI scanning is generally easy, but in the absence of 'red flag' symptoms, a normal, competently performed neurological examination almost excludes significant structural brain pathology.

Skin

New pressure sores on specialist wards are rare, but may occur on surgical wards and in nursing homes. All patients should be assessed for risk of pressure sores on admission to hospital; increasing age, impaired mobility and poor nutrition are risk factors for pressure damage. The sacrum, greater trochanters, and heels are most vulnerable. A sore can appear in as little as 30 minutes if a sufficiently immobile patient (e.g. after a hip fracture) is lying on a sufficiently hard surface. Shearing (from dragging across bedding) or maceration (usually from incontinence) are further mechanisms of skin damage. Specifically look at pressure areas, know the warning signs (non-blanching erythema or blisters), and how to stage a pressure sore (1: non-blanching erythema; 2: skin break; 3: full-skin thickness or subcutaneous tissue loss; 4: muscle cavity). Describe the extent and nature of dead tissue or slough, the state of the ulcer border (when healing, 'granulation tissue' looks moist and purple), and look for signs of infection.

Leg ulcers can be described similarly (but you have to take the bandages off first, and if you take them off be sure to have the means to dress them again).

Beware the cold, pale, numb, painful, acutely ischaemic limb, which needs urgent vascular surgical assessment.

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Pain

'Pain is what the patient says it is' (McCaffery, 1968). However, in someone with impaired cognition or communication, they may not be able to say, and pain may manifest as non-specific distress or a difficult behaviour, such as resistance to care, apathy, aggression, or calling out. We often use very abstract terms to describe pain (burning, stabbing, crushing, aching, and so on), which can be difficult for a person living with dementia. If the patient cannot localize or describe a pain, or if there is unexplained distress or agitation, it is necessary to look for it. A general survey of likely sites includes mouth, neck, joints, back, abdomen, constipation, urinary retention, skin, and genitals. Also observe the patient during transfers or walking, and discuss with family, carers, or nurses about pain during personal care. It is all too easy to miss fractures, including of the hips, pelvis, or neck of humerus.

Continence assessment

The commonest diagnoses will be unstable or overactive bladder and incomplete bladder emptying. A post-void bladder ultrasound scan and urine dipstick test provide the 'quick wins', but more involved assessment may include a neurological examination of the legs, inspection of the vulva for atrophy or prolapse, and a rectal examination for prostate enlargement and constipation.

Functional assessment

In someone who is fairly well, doctors can assess sit-to-stand, bed transfers, and gait. Anything more difficult is associated with risk, both to the patient (falling) and practitioner (back injury). Always be sure to follow your organization's manual handling policy. Nurses usually have good judgment about what someone can do, but you may require formal physiotherapy and occupational therapy assessments. Do not try to supervise a difficult transfer (e.g. to get someone on a bed) if you are not confident, or have not been trained. The golden rule is: if in doubt, use the safest transfer, using a hoist if necessary.

Investigations

Some people believe that frail older people are over-investigated. Others argue that age discrimination denies older people access to the best modern imaging technology. Rather than focusing on investigating more or investigating less, the most important thing is to investigate with a clear purpose. Older people with severe mental illness are particularly vulnerable to health inequality and suboptimal access to investigations and treatment for physical health problems.

Investigation is important in such cases since diagnosis may be more difficult due to non-specific and atypical presentation, multiple pathologies, and uncertain information, especially if history-taking is

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compromised by cognitive impairment or communication difficulties. This can mean that older people need more, not less, access to high-tech tests.

However, some tests are unpleasant, and most carry a cost, if only in terms of time, travel to hospital or the scanner, and inconvenience ('investigation burden'). For a frail, cognitively impaired or bewildered older person this can be a major trial. Tests done for defensive or academic reasons alone cannot be justified.

Tests provide information, which is valuable, but some argue that a test is only justified if it is going to change management. However, a test can be useful regardless of whether it leads to therapeutic intervention. A test result can inform prognosis, including reassurance when it is normal, or can help you decide to stop investigating further (for example, a scan reporting widespread cancer). If there is doubt about the wisdom of investigation, discuss with the patient and family and use the principles of shared decision-making to decide (options, pros and cons, how to weigh up the information) (Coulter and Collins, 2011). Clinical judgment is important, as is offering an opinion; it is unfair to put this professional responsibility onto individuals or families alone.

The practicality of tests must be considered and discussed. For example, retaining barium in the colon may be impossible, in which case colonoscopy is preferable. All bowel investigations are impossible without fully evacuating the bowel, which is unpleasant, and may itself require hospital admission. An MRI scan is impossible if there is a pacemaker or metallic implants (the scanning department will complete a safety questionnaire, and some implants are MRI-compatible), or if the person is too claustrophobic (up to 10%). If a test is judged to be absolutely necessary, sedation (usually with lorazepam) or a general anaesthetic may be justified if the patient is too agitated or fearful to allow it otherwise. No one benefits from an uninterpretable MRI scan degraded by movement artefacts.

Blood tests are less burdensome. Make sure there is a recent blood count, renal, liver and thyroid function, and calcium. Anaemia, neurological, and psychiatric symptoms in addition need vitamin B12 and folate measurement. C-reactive protein (CRP) is a useful screen for sepsis but (like temperature and the white cell count) is not 100% sensitive (there can be false negatives), nor specific (there are other causes), and sometimes the rise in CRP with infection is delayed up to 48 hours.

Dipstick urinalysis virtually excludes urinary infection when it is negative. Urinalysis positive for nitrites (suggesting presence of bacterial urease) and leucocyte esterase (suggesting presence of white blood cells) needs culture to confirm infection. Thirty per cent of elderly women, and anyone with a urethral catheter, will have asymptomatic bacteriuria, so the test must be interpreted in the light of circumstances and symptoms (which are unreliable in older people) (Ninan et al., 2014). If someone is non-

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specifically unwell and there is no other explanation, treating the urinary tract infection (UTI) is unavoidable.

Don't repeat tests unnecessarily. B₁₂ and thyroid function will not change over six months or a year. Don't measure vitamin D in someone on supplements (unless you suspect malabsorption).

Direct functional assessment

Doctors may watch someone walking or dressing, but allied health professionals routinely use a combination of self-report, informant information, and direct observation. This often comprises a combination of 'assessment' (ongoing or re-assessment) and 'therapy' (practice and intervention).

For example:

- A physiotherapist might assess transfers, walking, use of mobility aids, or ability to climb stairs.
- An occupational therapist may assess dressing, kitchen skills, or do a home visit to assess function in the home environment.
- A speech and language therapist will directly assess swallowing and communication, and use of communication aids.
- An audiologist will assess for and then teach and review use of a hearing aid.

Nurses use observations of physiological vital signs (alertness, pulse, blood pressure, temperature, oxygen saturation) to monitor physiology, and 'observation' of wellbeing, distress, ADL, oral intake, and behaviour. This often includes describing varying degrees of assistance. This represents valuable, if informal, 'assessment' and should be discussed in handover and multi-disciplinary team meetings.

Problem lists

A problem list is a way of assembling complex, disparate information to give an overview of concerns and where work needs to be done. It is usually a working tool, rather than a formal document.

Problems can be symptoms or impairments (e.g. breathlessness, weakness, spasticity, pain), diagnoses, disabilities (eating, mobility, continence, behaviours), social or environmental issues, abnormal test results, risks, or predispositions.

Use a problem list as part of the 'history of the presenting complaint', especially where there are many different symptoms. In sub-acute or long-term care settings (e.g. medical, MH, or rehabilitation wards, intermediate care or a care home) where more information has emerged from tests and assessments, and as issues develop over time, the problem list becomes a reassessment of 'where we have got to'. You may also use

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it at a ward round or weekly review. It is a way of making sure that things do not get overlooked.

Common problems

Immobility

Immobility is one of the 'geriatric giants' that comprise non-specific presentations of acute illness. It represents an 'activity limitation' or 'disability', and is often the consequence of multiple pathologies and other factors, such as volition and environment, although a single cause may be identified (Table 11.4). A common crisis occurs when someone has suddenly become more immobile ('gone off their legs') due to acute illness. Immobility also results from chronic illness, including musculoskeletal, neurological, or cardiorespiratory disease and dementia.

Table 11.4 Assessing immobility.		
System	Problem	Investigation
<i>Musculoskeletal</i>	Arthritis, especially knees, hips, back	Mainly clinical; X-ray may help
	Covert fractures (pelvis, hip, tibial plateau)	X-ray
	Limb loss	Clinical
	Foot deformities (toenails, ulcers, hallux valgus)	Clinical
	Myopathy	Vitamin D status, thyroid function, CK ^a , ESR ^b ; steroids
<i>Neurological</i>	Hemiparesis (usually stroke)	Clinical, CT ^c /MRI ^d brain
	Paraparesis (including spinal cord compression or ischaemia, cervical myelopathy)	MRI ^d spine, B ₁₂
	Parkinson's disease	Clinical

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	Peripheral neuropathy	Nerve conduction studies, glucose, B ₁₂ , ESR ^b , autoantibodies
<i>Vision</i>	Blindness	Clinical
	Hemianopia and inattention	Clinical, CT ^c brain
	Refractive error	Optician, glasses
<i>Cardiovascular</i>	Heart failure (breathlessness, oedema)	Clinical, chest X-ray, ECG ^e , echocardiography,
	Chest pain	Clinical, ECG ^e , chest X-ray, angiography
	Postural hypotension	Clinical, lying, and standing blood pressure
	Intermittent claudication	Clinical, duplex ultrasound, angiography
<i>Respiratory</i>	Breathlessness (COPD ^f , pulmonary embolism, fibrosis, effusion, pneumonia, cancer)	Chest X-ray, spirometry, blood gases, CT ^c thorax
<i>Skin</i>	Leg or foot ulcers	Clinical
	Oedema (dependency, heart failure, hypoalbuminaemia, venous or lymphatic obstruction)	Clinical, albumin, as for heart failure
<i>Psychological</i>	Anxiety, loss of confidence	Clinical
	Depression with psychomotor retardation	Clinical

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	Dementia (apraxia, executive failure)	Clinical
aCK: creatine kinase; bESR: erythrocyte sedimentation rate; cCT: computed tomography; dMRI: magnetic resonance imaging; eECG: electrocardiogram; fCOPD: chronic obstructive pulmonary disease.		

An important additional contributor to immobility is 'deconditioning': the loss of muscular strength and stamina, and cardiorespiratory fitness following a period of illness, immobility, or under-activity, sometimes over months or years. Loss of muscle mass and function is sometimes termed 'sarcopenia'. This is a particular problem during hospital admissions, when walking or other activity is not possible due to illness, discouraged or prevented due to fear of falls, or pointless due to lack of purpose or opportunity. Fortunately, deconditioning is reversible with sustained and progressive exercise (that is, exercise getting more difficult over time), and, along with restoration of confidence, probably accounts for a large part of what is achieved in general geriatric rehabilitation.

Gross mobility can be approximately quantified as a hierarchy of levels, from sitting balance, to transfers, through indoor mobility, stairs, outdoor mobility, and crossing roads or rough ground.

Further qualification can be in terms of:

- human help (number of persons, hands-on, or supervision)
- aids required (wheelchair, wheeled Zimmer frame, pulpit frame, gutter frame, three-wheeled delta frame, crutches, sticks)
- degree of difficulty experienced
- distance or speed achieved, e.g. timed walk or Timed Up and Go (TUG) test (Podsiadlo and Richardson, 1991).

A report may, for example, describe someone as being able to walk 15 metres with a Zimmer frame and the assistance of one person.

The medical role is to assess and identify causes, intervene to reverse treatable causes, palliate outstanding symptoms, and initiate rehabilitation to improve motor function and other functional abilities. Assessment will identify symptoms and signs causing the problem, which must then be explained by diagnoses. This requires history-taking and thorough examination of the neurological and musculoskeletal systems, heart, and chest. Reports from nurses and therapists can help to identify the immediate reasons why someone cannot walk. When mobility declines suddenly, consider an acute medical illness (infection, fracture, metabolic disturbance, new stroke, drug side-effect).

Immobility may not always be 'curable', but as a minimum we should not miss a treatable cause. If part, at least, of a progressive decline is due to deconditioning, this is eminently reversible. After an acute illness, the

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ambition should always be a return to pre-morbid mobility. Most direct restorative intervention will be directed and supervised by physiotherapists, nurses and care/healthcare assistants, or family.

Falls

Falls, and fear of falling, are common, and limiting. A third of older people fall each year, as do up to 60% of people living with dementia. Falls are inevitable if activity and mobility are encouraged; a complete absence of falls suggests inactivity or restraint. A fall can result in injury, which must be identified or excluded.

To assess someone who has fallen or who is at risk of falls, we must understand the balance system. Four mechanisms detect postural instability:

- vision
- the vestibular system
- proprioception in the neck, ankles, knees, and hips
- tactile sensation in the feet.

The motor and musculoskeletal systems provide the effector mechanism for adjusting to balance disturbances. The processor integrating sensory input and motor response is the central nervous system, acting through both reflex and intentional mechanisms. Balance is rarely static (e.g. standing still); posture must be maintained during walking, climbing stairs, and other activities, when we deliberately make ourselves unstable by moving our centre of gravity outside the base of support, and then react and compensate to maintain control. Anticipation, navigation, sequencing, planning, and judgment are required (visuospatial and executive functions). Abnormalities of any of these components increase the tendency to fall.

Falls may be classified in several ways.

By main cause (about a third each):

- Acute illness: falling is a non-specific presentation of any illness in an older person, so be vigilant for acute illness, such as pneumonia, adverse drug effect, arrhythmia, stroke, gastrointestinal bleed, metabolic or electrolyte disturbance.
- Chronic illness: especially neurological disease, including Parkinson's disease, stroke, and dementia, arthritis, cardiovascular problems, and visual problems.
- Environmental challenge (accidents, tripping, lighting).

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Pre-disposition and precipitation:

- Anyone can fall. What varies is the risks people take in order to do things, and the probability that any given activity, trauma, or insult will result in failure to maintain balance. People will also vary in the likelihood of a resulting injury.
- A long list of factors has been described that increase the risk of falls, including previous falls, chronic neurological disease, lower limb arthritis and proximal muscle weakness, abnormal gait, history of heart disease, postural hypotension, taking four or more prescription drugs (especially sedative, neuroleptic, and antidepressant medication), poor vision, and foot problems. The more risk factors, the greater the chance of falling, so interventions tend to be multifactorial to remove or reduce as many risk factors as possible.
- The precipitant may or may not be obvious. A single adequate explanation (seizure, syncope, acute stroke, heart attack, pulmonary embolus, trauma, tripping, misjudgment) should be sought, but will often be uncertain.

Syncopal or nonsyncopal, or association with dizziness:

- Syncope (loss of consciousness) has particular diagnostic implications (possible head trauma, cardiovascular, epileptic, hypoglycaemic causes; see Table 11.5)
- Syncope is associated with amnesia for the event in 30% of cases.
- Type of dizziness may give diagnostic clues. There are three main types, but dizziness is hard to describe, and precise classification may not be easy:
 - *presyncope* is 'light-headedness, as if about to faint', a 'swimming' sensation with blurred or darkened vision, and possibly tinnitus, and generally implies a cardiovascular cause.
 - *vertigo* is a spinning sensation, and implies vestibular or brainstem dysfunction.
 - *dysequilibrium* is a perception of unsteadiness, or staggering, 'as if drunk', which may be neurological or musculoskeletal in origin. Brief (few seconds) dysequilibrium occurs when the (arthritic) neck is extended during standing (NB: ENT surgeons sometimes use the term 'disequilibrium' to mean vertigo!).

Table 11.5 Causes of syncope and pre-syncope.

Factor	Comment	Investigation
<i>Head trauma</i>	Usually obvious. Look for lacerations.	CT ^a brain if intracranial bleeding suspected (drowsy, features of

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	Beware cervical spine injury	raised intracranial pressure, focal neurology) or on anticoagulants.
<i>Epilepsy</i>	Generalized seizures are defined by loss of consciousness. Get an eye-witness description. Ask about ictal and post-ictal features.	CT ^a brain, glucose, electrolytes, EEG ^b .
<i>Intracranial bleeding</i>	Primary or subarachnoid haemorrhage. Highly unlikely to be transient, unless it precipitates a seizure	CT ^a brain, +/- angiography.
<i>Hypoglycaemia</i>	Loss of consciousness only if severe, unless it precipitates a seizure	Capillary blood glucose
<i>Vasovagal syncope</i>	3Ps: provocation, posture, prodrome.	Clinical diagnosis, exclusion of other causes
<i>Postural hypotension</i>	Due to drugs, autonomic neuropathy, e.g. in diabetes, or age- or dementia-related autonomic dysfunction	Lying and standing BP, or head-up tilt test; Autonomic function tests
<i>Carotid sinus hypersensitivity</i>	Cardioinhibitory and vasodepressor types	Head-up tilt test.
<i>Other provoked syncopes</i>	Micturition, defaecation, cough	Clinical diagnosis
<i>Bradyarrhythmias</i>	Heart block, Stokes-Adams attacks, sick sinus syndrome	ECG ^c , 24h ECG ^c

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<i>Tachy-arrhythmias</i>	Sustained or paroxysmal, AF ^d , SVT ^e , VT ^f	ECG ^c , 24h ECG ^c
<i>Tight aortic stenosis</i>	Typically exertional syncope (but uncommon)	Echocardiography
<i>Acute myocardial infarction</i>	Temporary or permanent myocardial damage and pump failure; provoked transient arrhythmia; vasovagal secondary to pain.	ECG ^c , troponins, cardiac enzymes

^aCT computed tomography;

^bEEG electroencephalogram;

^cECG electrocardiogram;

^dAF atrial fibrillation;

^eSVT supraventricular tachycardia;

^fVT ventricular tachycardia

Falls assessment needs to be multi-disciplinary:

- The predisposition and precipitant model is most helpful. First, explain the fall, what happened, and why? Then identify what risk factors make the person prone to falling.
- A history from a witness is required if there was syncope, an unexplained fall, or no recall.
- Identify the circumstances of the fall. What was the person doing? Was there a clear and sufficient cause (tripping, being pushed, falling out of bed, standing without habitually required supervision)?
- Was there any warning? Did the person complain of feeling dizzy? Was there time to sit down? Or did the patient drop to the ground?
- What did they look like? Cardiovascular causes often cause a 'deathly pallor'. Generalized epilepsy causes transient respiratory arrest, and the patient may go blue. Convulsion (shaking), tongue biting, or incontinence may be evident.
- Were there associated symptoms such as chest pain, palpitation, or breathlessness?

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- Did anyone take the pulse during the episode?
- Enquire if it has happened before. If so, how often? Were there obvious precipitants?
- Ask if acute or chronic alcohol excess involved?
- Assess general function, including transfers, walking, stairs, outdoor mobility, dressing, and bladder function (hurrying to the toilet can lead to lapses of judgment; nocturia is another occasion of risk).
- Examination during a syncopal episode is invaluable, especially for features of a seizure; take pulse, blood pressure, ECG rhythm strip if available, respiratory rate, or neurological signs
- Between attacks a thorough cardiovascular, neurological, musculoskeletal, and ear examination is required.
- Check postural blood pressure.
- Examine for heart murmurs, suggesting aortic stenosis or other structural abnormalities, e.g. hypertrophic cardiomyopathy. Get an echocardiogram if suspicious.
- Test visual acuity (separately in each eye) and examine for cataracts. Are the spectacles up to date? Bifocal or varifocal lenses increase the risk of falling.
- Test visual fields, and for visual inattention. Examine for Parkinsonism (cogwheel rigidity, best felt at the wrist), bradykinesia (touch the thumb on each finger in turn), and tremor. Examine for pyramidal (upper motor neurone) lesions—weakness, increased tone and reflexes, up-going plantar response (Babinski's sign). Pronator drift is a sensitive test for subtle weakness. Also test proximal muscle power (shoulder abduction, hip flexion) and for lower limb sensation loss (pin prick, vibration, proprioception).
- Test cerebellar function (finger–nose ataxia, dysdiadochokinesia).
- Examine the neck for cervical spondylosis, hips and knees for arthritis (unsteadiness either due to mechanical instability or 'nociceptive inhibition', giving sudden loss of supporting muscle tone around an acutely painful joint).
- Examine the feet for overgrown toenails (onychogryphosis), corns, calluses, ulcers, and other deformities.

There are some important caveats in assessing falls:

- Transient ischaemic attacks (TIA) do not cause syncope or presyncope.
- Isolated vertigo (with no other associated neurological features) is usually due to vestibular dysfunction.
- Hyperventilation can cause dizziness (symptoms are reproduced by hyperventilating).

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- Vasovagal syncope always occurs standing up, and there is a clear precipitant (pain, fear, smell) and some presyncopal warning symptoms before the loss of consciousness.

The choice of tests will be guided by prior assessment (Table 11.5):

- The diagnostic yield of echocardiography and 24-hour ECG is low, and these tests should not be used indiscriminately in the absence of appropriate findings from the history, clinical examination, or 12-lead ECG. A 24-hour ECG recording can be difficult to interpret, as they often show minor abnormalities of no particular diagnostic value, or there may be false negatives. If the clinical features are sufficiently suspicious, 48- or 72-hour recordings can be done, or an implantable loop recorder inserted (like a pacemaker that can be remotely interrogated)
- CT or MRI scanning is only required when specifically indicated. Fits require neuroimaging. Possible bony injury resulting from falls requires appropriate imaging.

Environmental assessment and modification, usually by an occupational therapist, to reduce hazards, optimize equipment and appliances, and review lighting, are commonly employed in falls prevention programmes.

Bony injury is painful, and fractures are usually severely painful, although this can be difficult to assess if the patient has communication impairment. The only way to exclude a fracture is an X-ray (or other imaging), which involves a disruptive trip to hospital and the possibility of an escalating cascade of assessment and precautionary admission. Someone who can weight bear through a limb is unlikely to have fractured it, and although a pelvic or vertebral fracture is possible, management of these is usually conservative. Arthritic joints hurt more after trauma, and this usually persists for several weeks. Muscle or ligamentous injuries are also possible, and recover over four to six weeks with analgesia and progressive return to normal activity.

Head injury is worrying because of the possibility of intracerebral haemorrhage. Subdural haematoma can occur after minimal or unnoticed trauma, and if significant will result in fluctuating drowsiness, focal neurological signs, or increased confusion. Subdurals are potentially operable but, as a general rule, frail patients over 80 do not tolerate neurosurgery well. Other haemorrhagic conditions, including cerebral contusion or traumatic subarachnoid haemorrhage, can result from falls, but are managed conservatively. The only way to tell for sure is to do a CT head scan. It is also possible that an intracerebral haemorrhage or aneurysmal subarachnoid haemorrhage caused the fall. Risks are greater, and the threshold for CT scanning reduced, in those on anticoagulants.

Prolonged lying after a fall may result in pressure sores, rhabdomyolysis (with greatly raised CK), which can lead to acute kidney injury and hypothermia and indicates cognitive impairment or social vulnerability.

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Incontinence and lower urinary tract symptoms (LUTS)

Like other non-specific presentations of acute illness, new incontinence can be caused by any acute illness, and is not necessarily confined to those affecting the urinary tract. To determine if the incontinence is new requires a history of what went before. So-called 'transient' urinary incontinence should resolve with the underlying illness.

To diagnose a UTI requires evidence of systemic infection (temperature, raised CRP or white cell count), and some evidence of involvement of the urinary tract (dysuria or frequency, or a positive urine culture). Heavy pyuria is suggestive. A negative dipstick test for leucocytes, nitrites, blood, and protein more or less rules out UTI. A positive dipstick test is insufficient by itself to diagnose UTI; follow-up with culture is required. About 30% of older women have asymptomatic bacteriuria, which does not require antibiotic treatment. Defining what is truly 'asymptomatic' can be difficult, if the clinical presentation is non-specific (such as a fall or delirium), in which case treatment is unavoidable. Not all incontinence or delirium is caused by UTI, but a dipstick test, and culture if positive, is mandatory. Over-diagnosing UTI leads to other things being missed (Ninan et al., 2014).

'Functional incontinence' is wetting caused because of immobility, communication difficulties, disorientation, or inability to find a toilet (especially after stroke or for a person living with dementia in a new environment or strange hospital ward), rather than because the bladder is abnormal.

The majority of longer-term bladder problems among older people is caused by detrusor instability (overactive bladder), followed by incomplete bladder emptying (retention). Urgency and nocturia can be almost as troublesome as incontinence itself. Urologists have a saying that 'the bladder is an unreliable witness', meaning that it is difficult to make accurate diagnoses from symptoms alone. The cardinal feature of an overactive bladder is urinary urgency (inability to postpone the need to void). Urgency may be brought on by trigger factors: arriving home (the 'key in the door phenomenon'), bumpy rides, or the sound of running water. Other symptoms include urinary frequency and nocturia. Many cases represent primary detrusor instability (no evident precipitating cause), but other causes include any neurological disease (including stroke, dementia, and multiple sclerosis, and in which case it may be called 'hyperreflexia'), prostatic hyperplasia, bladder infections, cancers and stones, and oestrogen deficiency. Fast filling also provokes unstable bladder contractions, such as after drinking several cups of caffeinated drinks or alcohol, or taking loop diuretics.

Examination has a limited role, apart from excluding neurological disease and feeling for an enlarged bladder and prostate gland per rectum (but these are poor guides). Women may be examined for atrophic urethritis, but essentially all older women are oestrogen deficient. The gold

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standard for diagnosis is cystometry (bladder pressure studies), which is invasive and unpleasant, but may be useful if an enlarged prostate is responsible. A frequency-volume chart over three days gives a lot of information, including functional bladder capacity (normal is 350–600ml), which is likely to be low (150–250ml) in detrusor instability, frequency (less than seven times by day and once at night is normal), and the day/night split of urine production.

Some people with incontinence, especially in dementia, will not be cured, and a routine of prompted voiding (about every two hours), along with adequate containment is the best that can be achieved. However, in assessment, it is important not to miss infection, the effects of drugs, or retention.

Nocturia is a troublesome problem for older people, resulting in disturbed sleep and falls. About half of women over 70 pass urine two or more times at night. There are many 'medical causes', including diabetes, heart failure, especially with leg oedema, hypercalcaemia, alcohol or tea drunk in the evening, and taking lithium drugs that must be identified. Many are due to age-related nocturnal polyuria, due to a combination of loss of diurnal production of antidiuretic hormone and renal insensitivity to it. A day/night split with more than a third produced at night is diagnostic (in younger adults, urine production halves during sleep).

Incomplete emptying is easy to assess with the use of portable ultrasound scanners. These must be used post-void. Anything less than 100ml is normal, although symptoms are unlikely with volumes less than 300mls residual. A residual volume over 100ml precludes the use of anticholinergic bladder-stabilizing drugs, however. Causes include anticholinergic drugs, prostatic enlargement, faecal impaction, spinal cord disease and detrusor failure. Check renal function and prostate specific antigen, and do a rectal exam (or abdominal X-ray) to assess for faecal loading (as well as examining the prostate).

'Obstructive' urinary symptoms may be reported by men including poor stream, hesitancy (slowness to get started), intermittency (stop-start flow) and terminal dribbling. A urine flow rate (the urology clinic will have a machine), cystoscopy, or cystometry are used to make the diagnosis formally.

Faecal incontinence may be due to diarrhoea, which requires investigation in its own right. Describe the stool type using the Bristol Stool Scale (Lewis and Heaton, 1997). Do not miss cases caused by drugs or laxatives. Such is the desire among healthcare professionals to avoid constipation that laxatives are now the commonest cause of faecal incontinence in care homes. Faecal incontinence can be due to constipation with overflow; the rectum produces mucus, which gets stained with faeces and passed as 'spurious diarrhoea'. More commonly, a disinhibited 'neurogenic' colon (equivalent to the unstable bladder) can be caused by neurological disease or dementia (Box 11.1). This is a

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diagnosis of exclusion. For the most part, toileting while trying to predict bowel movements and containment are all that can be done, apart from a 'bowel regime' (constipate with loperamide and electively evacuate with an enema, which is unpleasant and generally disliked by patients unless it is the only way to remain at home). Using a diary may help to identify patterns.

Box 11.1 Causes of faecal incontinence

- Diarrhoea
- Laxatives or other drugs
- Disinhibited 'neurogenic' colon
- Constipation with overflow incontinence
- Anorectal sphincter damage (usually childbirth or surgery)
- Immobility
- Diminished level of consciousness or unawareness

Stroke

Stroke is a syndrome of sudden onset (or rapidly progressive over 24h) focal neurological deficit of presumed vascular origin. A newer, pathologically based definition is 'focal brain injury caused by sudden interruption of blood flow'. TIA is a stroke that gets better quickly, usually within the hour, by definition within 24 hours. The importance of TIA (and other minor stroke) lies in its propensity to recur (8% within a week, 17% within three months), necessitating rapid investigation and institution of secondary prevention measures.

The clinical manifestations depend on the site of the injury and include hemiparesis, hemisensory loss or hemi-neglect, visual field loss, speech and swallowing disorders, cranial nerve palsies, incoordination, and cognitive impairment.

Stroke is a syndrome: a collection of signs and symptoms. The first diagnostic task is to exclude mimics (including hypoglycaemia, fits, migraines, tumours, old stroke made worse by intercurrent illness). The next task is to distinguish an infarct from a bleed, which requires early brain imaging (preferably immediately, certainly within 24 hours). This has assumed a new urgency with the availability of thrombolytic therapy for use within 4.5 hours of onset for infarcts ('brain attack').

Stroke diagnosis requires a mechanism or explanation to be defined, although no convincing cause is found in up to half of fully investigated cases. Defining stroke subtypes (e.g. using the Oxford clinical system:

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total anterior circulation (TACS), partial anterior circulation (PACS), lacunar (LACS) and posterior circulation (POCS)) can help define both cause and prognosis. A TACS is due to an occlusion of the middle cerebral artery (MCA), and so damages cortical and subcortical structures, including hemiparesis, visual field loss, and higher cortical function (and often drowsiness). A PACS is due to an MCA branch occlusion, comprises fewer than the full set of TACS features, and is often embolic (from the heart or a carotid plaque). Lacunar strokes (pure motor or sensory hemi-symptoms) involve small end arteries to the internal capsule, typically in hypertension, diabetes, and smoking. Posterior circulation strokes involve the occipital cortex (isolated hemianopia), cerebellum (isolated cerebellar syndrome), or brain stem (sometimes damaging cranial nerve nuclei with contralateral hemiparesis).

Investigation requires assessing cardiac rhythm and looking for evidence of ischaemic damage to the heart (ECG), examining the carotid or vertebr basilar arteries for occlusion, stenosis, or dissection (duplex ultrasound or MR/CT angiography), and assessing other vascular risk factors. In younger patients with no obvious cause, a bubble contrast or trans-oesophageal echocardiography study can identify patent foramen ovale and atrial septal aneurysms. Rare, but diagnostically important, causes include endocarditis (clinical signs, temperature, inflammatory markers, blood cultures, echocardiography), and arteritis (specifically temporal arteritis, with headache and high ESR).

Intracerebral bleeds may need investigation with MR or CT angiography (for aneurysms or vascular malformations) or interval rescanning (for tumours or vascular malformations), although in older people many deep bleeds are put down to hypertension, while superficial (lobar) bleeds are attributed to amyloid angiopathy (especially common in Alzheimer's disease). Bleeds may also occur into areas of old infarction. Watch for patients on anticoagulants; anyone on warfarin or newer anticoagulants with new neurological signs or a persisting headache needs urgent CT head scanning; if there is bleeding, the anticoagulation should be reversed immediately.

Parkinson's disease

Parkinson's disease is one of a group of 'akinetic rigid' syndromes, and one cause of extrapyramidal motor symptoms. Other diagnoses include multi-system atrophy, progressive supranuclear palsy, cerebrovascular disease, dementia with Lewy bodies, corticobasal degeneration, and the adverse effects of antipsychotic and some other drugs. All have prominent associations with cognitive and neuropsychiatric features.

The key feature is bradykinesia, or slowness of movement: you cannot diagnose Parkinson's disease without this sign. It is assessed in repeated movements such as touching each finger to the thumb in turn. Other core features are: increased muscle tone, usually with a 'cogwheel' pattern; a 4–6 Hertz 'pill-rolling' tremor, evident at rest and suppressed by activity

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(but re-emerging on sustained posture such as holding up the arms); and postural instability. Onset is unilateral, but progresses to both sides. Mask-like face, a quiet mumbling dysarthria, seborrhoea, stooped 'festinant' gait with problems initiating a step, and swallowing problems are also seen. In idiopathic Parkinson's disease, 70–100% of patients respond to treatment with L-dopa drugs or dopamine agonists.

In the initial stages, treatment can be very successful, but as time goes by problems emerge, including fluctuation or end-of-dose effects, dyskinesias (writhing movements), and freezing episodes (suddenly stopping and not being able to restart). Functional assessment (occupational therapy and physiotherapy) are required with a view to optimizing mobility and adapting to emerging problems.

Cognitive disorders are very common, especially executive dysfunction, and often progress on to dementia. 'Parkinson's disease dementia' and DLB behave similarly, and probably represent a continuum. In addition, delusions or hallucinations may emerge or be precipitated by drugs (especially the dopamine agonists such as ropinirole and pramipexole, which must be used with extreme caution, or not at all, in people with dementia).

Hip fracture

A hip fracture results from an interplay of three things:

- Trauma, usually a fall (only 1% of hip fractures are spontaneous)
- Sufficient impact (and 'correct' geometry) to break the bone
- Bone that is weak enough to break, usually due to osteoporosis, but sometimes due to a metastasis.

The incidence of hip fracture increases exponentially with age. A third of victims are dead within a year of a hip fracture. Only half of survivors regain their previous mobility. Half of people with a hip fracture have a history of dementia. Fifteen per cent have delirium at presentation and up to half develop it after surgery. Proactive management by a geriatrician alongside the orthopaedic surgeon ('orthogeriatrics') dramatically reduces the risk of delirium (Marcantonio et al., 2001), and complications or distress among people living with dementia (Smith et al., 2015). Comorbidity and acute medical complications are very common, and are associated with mortality.

Assessment should include:

- Identifying why the patient fell, and whether intervention is required to prevent further falls.
- Identifying and optimizing comorbidities, and rationalizing medications.

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- Assessment of osteoporosis—it is safe to assume that all older people with a hip fracture are osteoporotic. Seek a secondary cause: post-menopausal women, hypogonadism in men, steroid drugs or Cushing's syndrome, thyrotoxicosis, smoking, alcoholism, myeloma, hyperparathyroidism, check vitamin D status. Consider drug treatment options (single dose intravenous zoledronic acid is convenient for very frail patients; oral bisphosphonates are difficult to take and prone to cause adverse effects).

Polymyalgia rheumatica (PMR)

Polymyalgia rheumatica (PMR) is almost unheard of under the age of 50, and is one of a small number of pure disorders of ageing. It presents with pain and stiffness around the shoulders or hips and buttocks, worse in the morning, sometimes quite disabling. It may be undiagnosed for months as it is ascribed to arthritis, age, or other comorbidity. In those with appropriate symptoms, the diagnosis is confirmed by a greatly raised ESR, and a rapid response (within 48 hours) to high-dose prednisolone (30mg/d, but rheumatoid arthritis may also rapidly respond to steroids). Thirty per cent also have temporal arteritis, where the urgency is greater, as optic ischaemia or stroke can occur. Ask about headache (possibly unilateral) and palpate the temporal arteries. Arrange for temporal artery biopsy if there is doubt.

Osteoarthritis

Osteoarthritis is the commonest disabling physical condition in Western populations, is evident in most very elderly people, and often ignored by their doctors. Arthritis contributes to immobility, falls, depression, and deconditioning. Examine the joints, exclude inflammatory arthropathies, assess function, and consider therapy options, starting with analgesia (paracetamol and work upwards, using low doses of strong opioids if necessary) and joint-stabilizing muscle strengthening. Involve a physiotherapist and occupational therapist. Assess for aids and appliances, and consider arthroplasty.

The end of life

If someone is about to die, it is useful to know, so that plans can be made, families forewarned, and treatment reprioritized.

Twenty-eight per cent of deaths are associated with cancer, and are relatively predictable once the cancer is disseminated, and functional performance ('performance status' or Karnofsky score) starts to deteriorate. Otherwise, many deaths are associated with dementia or organ failure, including heart, lung, or renal failure; making predictions is much less reliable in these conditions. Comorbidities are as likely to impact on function as the primary condition leading to death. Care is required: delirium or impairment in function associated with acute illness

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can look like impending death, and in some cases survival and worthwhile functional recovery occurs.

Diagnosing dying in chronic conditions is far from easy. A person with heart or respiratory failure who is breathless at rest or on minimal exertion, or who has frequent hospital admissions with exacerbations, is likely in the last year of life. Someone with dementia who is mute, immobile, incontinent, struggling to eat, or whose appetite has failed is usually dying. In dementia, loss of appetite and aspiration during swallowing are particularly poor prognostic signs (but assess for potentially treatable causes such as drug adverse effects, mouth problems, including candidiasis and poor dentition, intercurrent infection, and constipation). Half of people with MH conditions admitted to an acute hospital are dead within a year.

There are some scales that attempt to provide guidance for clinicians, including the Minimum Data Set Mortality risk index (Porock et al., 2010) and the eFI (Clegg et al., 2016). None of these is sufficiently valid to guide individual cases. The difficulty is in identifying exactly who is about to die, but the principles of palliative care are applicable to many frail or disabled older people, and show considerable overlap with person-centred care and CGA models, and the best way to manage a 'problem' will often be to treat the underlying medical diagnosis causing it. Care will necessarily remain eclectic or 'twin' (or 'multi') track. Bronchopneumonia is the most frequently cited cause of death in people with Alzheimer's disease (Duthie et al., 2011).

However, there may be treatable causes that can mislead the unwary. One study investigating why end-of-life care models were less successful in non-malignant conditions found that practitioners had so often 'had their fingers burnt' in making prognoses that turned out not to be true, that they rapidly became cautious or reluctant (Elliott and Nicholson, 2017).

Principles of palliative care include:

- Open communication, including about likely approach of the end of life and uncertainties in making predictions.
- Setting of priorities ('what matters?'), often around relieving distress and maximizing function, the avoidance of burden on family, and maintenance of dignity.
- Identification of problems and symptoms, identifying causes or likely mechanisms of the problems, and using medical or therapy interventions to overcome them.
- Shared decision-making.
- Minimizing treatment, investigation, and healthcare burden (such as attending multiple clinics or appointments, or adverse treatment effects).

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- Identifying and addressing psychological, social, and spiritual problems, including engaging families and other stakeholders.
- Making plans for the future, including preferred place of care, and times when hospital admission may or may not be appropriate.

Typical problems include symptoms, such as pain, difficulties with appetite and swallowing, incontinence, loss of mobility and function, dependency on others, polypharmacy and deprescribing, the burden of delivery of 'routine' care (such as pressure area care and observations), and dealing with mental distress and behaviours. Assessment (and ongoing re-assessment) is central to this. It may be family or professionally led, and will often include care home staff.

Advance care planning in dementia should be supported, particularly while the person with dementia is able to take part. This may be associated with more positive experiences at the end of life, and can reduce the decision-making burden faced by carers (Barker et al., 2017; Dixon et al., 2018).

Conclusion

1. Older people may present with non-specific or atypical symptoms. They often have multiple pathologies, tend to lose functional abilities relatively quickly, and are prone to complications. Their care needs explicit rehabilitation and consideration of their environment.
2. The medical goal in assessing an older person is to explain (all) their problems in terms of diagnoses. This needs patience, commitment, thoroughness, and time. Medical history often requires review or expansion, and examination may have to be spread over more than one session and combined with observations from families, nurses and therapists.
3. There are many practical problems to history-taking. Practitioners require skills to facilitate the process for aphasic, cognitively impaired, deaf, or non-English-speaking patients.
4. Third-party history (or histories) will be required for many patients, especially those presenting with a debilitating episode of mental illness, or where there is cognitive impairment, aphasia, syncope, or unexplained falls.
5. Drug history is crucial and may need some effort to obtain.
6. Full social and functional histories are required, in particular, living arrangements, accommodation type, and help available or used. Function is summarized in eating, mobility, continence, and behaviour, but a very wide range of activities should be considered, tailored to the individual being assessed.
7. Aspects of physical examination that are often neglected include postural blood pressure, joints, vision, and nervous system.
8. Investigations should be used with discretion, but difficulties and complexities in diagnosis make access to high-tech tests more, rather than less, necessary for older people.

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9. Doctors must support multiprofessional working, taking account of other professionals' assessments and observations, providing help in terms of diagnostic explanation and assessment of problems or complications identified by nurses or therapists, and respecting other professionals' expertise.
 10. Problem lists help catalogue multiple problems and map areas of uncertainty.
 11. Immobility, falls, confusion, and incontinence are all syndromes or disabilities that require explanation, diagnosis, and assessment of where intervention might help.
 12. Identifying the approach of the end of life can be difficult, but is useful in making plans and reprioritizing the goals of medical care. There is considerable overlap between end-of-life care, comprehensive geriatric assessment, and person-centred dementia care.

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Neuroimaging

Chapter: Neuroimaging

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Introduction

With dramatic developments in imaging technology over the past few decades, there has been a surge of neuroimaging research studies, particularly in old age psychiatry. Age-related brain changes, together with specific pathological abnormalities, have generated a host of case-control studies that illuminate the aetiology and pathophysiology of brain disease. However, little has as yet been translated into clinical practice. While cutting-edge imaging protocols have the potential to be translated into the clinical domain, they still lack a realistic estimation of sensitivity, specificity, and predictive power that typically comes from studying large-scale representative groups with a validated diagnosis. To cover this division of neuroimaging into scientific clinical enquiry and clinical routine, the first section of this chapter aims to provide a brief overview of the theory behind neuroimaging techniques and outline commonly

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used analysis methods. The second section covers the current and future clinical applications of neuroimaging. Particular focus is given to the role of neuroimaging in making a diagnosis, predicting outcome, and understanding illness mechanisms.

Theory

Computed X-ray tomography

Computed tomography (CT) is based upon the degree of attenuation of X-rays in neural tissue, i.e. their electron density. Attenuation is greater in hyperdense tissues such as bone, which consist of calcium, phosphate, and carbonate minerals and appear white in a CT image, compared with hypodense tissues, e.g. cerebrospinal fluid (CSF), which primarily consists of water and appears dark. Compared with magnetic resonance imaging (MRI), soft tissue contrast is low, and dense bony structure can obscure underlying soft tissue signals (e.g. in posterior fossa). The development of spiral CT scanners has provided significantly improved resolution and speed of scanning, also resulting in a reduced radiation dose.

Magnetic resonance imaging (MRI)

MRI is a non-invasive technique that can provide high resolution in vivo images of the brain. Different MRI sequences allow various aspects of the brain's structure and function to be investigated. Grey matter is most commonly studied using T₁-weighted MRI (Fig. **12.1a**), white matter hyperintensities (WMH) using T₂-weighted MRI or fluid attenuated inversion recovery (FLAIR) images (Fig. **12.1b,c**), neuronal activation patterns using functional MRI (fMRI) (Fig. **12.1d**), white matter microstructure using diffusion tensor imaging (DTI) (Fig. **12.1e**), cerebral perfusion using arterial spin labelling (ASL) (Fig. **12.1f**) and biochemical profiles using MR spectroscopy (Fig. **12.7**).

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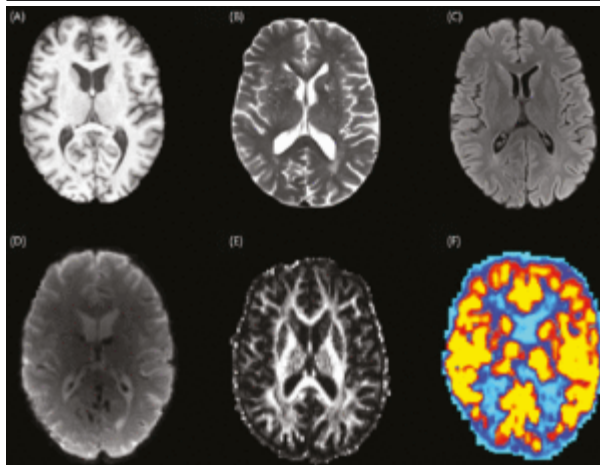


Fig. 12.1

Multi-modal MRI. Examples of (A) T_1 -weighted image, (B) T_2 -weighted image, (C) FLAIR image, (D) a resting-state functional blood oxygen level dependent (BOLD) image, (E) a fractional anisotropy (FA) map derived from a diffusion tensor imaging scan, and (F) a cerebral perfusion map derived from an arterial spin labelling scan. All images are presented in the axial plane and prepared using data from the Whitehall II Imaging Sub-study.

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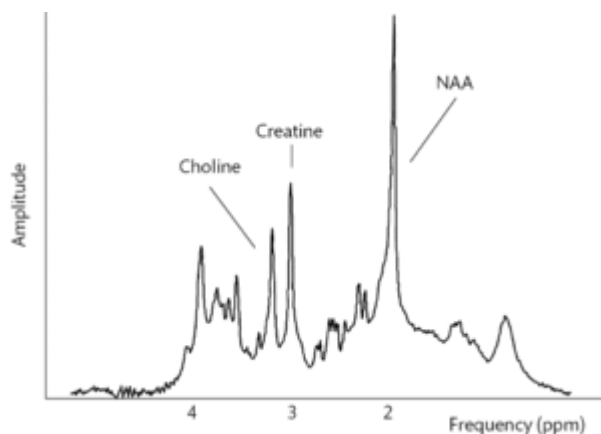


Fig. 12.7

Proton MRS Spectrum. Choline (cell membrane marker); Creatine (energy metabolism); NAA, n-acetyl aspartate (neuronal marker).

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The physical principles of MRI are generally based upon the nuclear MR of protons present in water within the tissue. Protons possess magnetic spins that, in the absence of a magnetic field, are randomly oriented. An

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MRI scanner consists of a large magnet that exerts a powerful external magnetic field (B_0) in which spins align to create net magnetization along B_0 . During an MRI scan, a second magnetic field called the radiofrequency pulse is applied, causing the net magnetization to tilt away from B_0 and along the direction of the transverse radiofrequency field. The subsequent removal of the radiofrequency pulse causes the protons to realign themselves such that their net magnetic moment is again parallel to B_0 . The return to equilibrium is called *relaxation*, during which the protons lose energy by emitting their own radiofrequency signal. This is the signal that is reconstructed to produce an MR image, and can be detected with a radiofrequency-tuned coil.

The intensity of the MR signal depends on several factors, including proton density, the relative timing of external radiofrequency pulses, the rate of recovery of magnetization along the longitudinal axis (defined by the relaxation time constant T_1), and the loss of magnetization in the transverse plane (defined by the relaxation time constant T_2). Since proton density, T_1 , and T_2 are tissue-specific properties, they can be manipulated by varying the timing of radiofrequency pulses (repetition time, TR) and the time between transmitting a radiofrequency pulse and measuring a signal (echo time, TE) in order to differentiate between grey matter, white matter and CSF on an MR image. The spatial location of the MR signal is encoded by imposing magnetic gradients on B_0 so that each part of the brain is subjected to a slightly different field strength and therefore has its own resonance radiofrequency. Thus, in addition to differentiating between the *types* of tissues, the intensity of the signal at each frequency also carries information about the *position* of the tissue within the scanner and can be used to define spatial localization.

T₁-weighted MRI

The strength of the T_1 -weighted signal is determined by the amount of magnetization that is restored along B_0 after the radiofrequency pulse is applied. T_1 relaxation time varies depending on the type of tissue in the brain and how freely protons can move within the tissue. CSF has the longest T_1 relaxation time, followed by grey matter, and then white matter, which has the shortest T_1 . This difference in T_1 relaxation between tissues means that when the external radiofrequency pulse is removed, magnetization is restored slowest in CSF (high T_1) and fastest in white matter (short T_1) before the next pulse is applied. T_1 -weighted images typically have a short TR (repeat time) between radiofrequency pulses. With a short TR, there is limited time for all tissues to fully restore net magnetization along B_0 before their magnetization is flipped again. This creates a significant discrepancy in the amount of restored magnetization in each tissue type. CSF, which restores the least magnetization along B_0 before the next pulse, has the lowest MR signal intensity and appears black on a T_1 -weighted image. By comparison, white matter, which is able to quickly restore more magnetization along

B_0 before the next pulse, has the highest MR signal intensity and appears bright on the image.

T_1 -weighted MRI is the preferred modality to isolate and examine grey matter. The most common research analysis techniques use region-of-interest (ROI) and voxel-based morphometry (VBM). ROI analysis of grey matter volumes can be used to test a specific hypothesis about a particular brain region and has advanced from tracing brain regions by hand to employing fully automated segmentation methods (Babalola et al., 2009). Furthermore, shape analysis techniques can provide greater detail of the location of structural changes in subcortical structures (Styner et al., 2003; Patenaude et al., 2011).

VBM provides an assessment of grey matter across the whole brain and can be used for exploratory analyses with no a priori information about the location of potential grey matter differences. VBM typically involves: segmentation of T_1 -weighted images into grey matter, white matter, and CSF; registration of each subject's scans into a standard template to make them comparable between different subjects; optional intensity modulation of images to compensate for the amount of expansion or contraction of each image; and spatial smoothing of images (Ashburner and Friston, 2000; Good et al., 2001). These preprocessing steps allow for standardization of the images and mean that a voxel-by-voxel whole-brain statistical comparison of grey matter can then be made between subjects, between diagnostic groups, and along dimensions, e.g. age or cognitive function. However, as a consequence, VBM is limited by the quality of between-participant image registration and the amount of spatial smoothing of data (Bookstein, 2001).

T_2 -weighted MRI/FLAIR

T_2 -weighted images are obtained by exploiting tissue-specific differences in T_2 -relaxation times. As discussed, T_2 -relaxation time relates to the decay of the transverse magnetization produced by the radiofrequency pulse (T_2 in ms: CSF > grey matter > white matter). In T_2 -weighted images, white matter, which has the shortest T_2 time, loses signal the fastest and therefore appears dark grey, whereas CSF appears white and grey matter appears light grey. Pathological changes often stand out as bright white signals (hyperintensities).

Periventricular and deep WMH were traditionally assessed using visual rating scales on T_2 -weighted scans, although it can be difficult to differentiate between periventricular WMH and CSF on T_2 -weighted images. Fluid attenuated inversion recovery (FLAIR) scans are typically used alongside, or instead of, T_2 -weighted images in the assessment of WMH (Wardlaw et al. 2013). FLAIR sequences increase the contrast between CSF and WMH by nulling the signal from CSF and make it appear black on the MR image, therefore improving the recognition of periventricular WMH (Fig. **12.1c**). Recent advances in automatic segmentation tools allow reliable objective quantifications of total WMH

volumes and the ability to distinguish between deep and periventricular WMH without the need for manually tracing the lesions or relying on subjective visual ratings (Griffanti et al., 2018; Griffanti et al., 2016).

Functional magnetic resonance imaging

Functional MRI (fMRI) provides an indirect measure of neural function by measuring the haemodynamic response to neuronal activity. During neuronal activation, there is an increase in the extraction of oxygen from the blood vessels into the neuron, and a heightened rate of oxygen metabolism within the neuron. This triggers an increase in local cerebral blood flow that far exceeds the rate of oxygen metabolism, resulting in an abundance of oxygenated blood in the vessels surrounding the active tissue. The intensity of an fMRI image is derived from this local change in blood oxygenation, which creates the blood oxygen level-dependent (BOLD) signal.

Oxygenated (oxy)haemoglobin is diamagnetic (i.e. has a stronger BOLD MR signal), whereas deoxygenated (deoxy)haemoglobin is paramagnetic (i.e. has a weaker BOLD MR signal). The higher oxy-to-deoxyhaemoglobin ratio that results from neuronal activity leads to a decrease in magnetic susceptibility and an increase in the BOLD signal (Matthews and Jezzard, 2004).

The majority of fMRI studies have compared the BOLD signal between a baseline and an activation condition. Particularly relevant to psychiatric research are fMRI experiments that assess activation during cognitive tasks or exposure to emotional stimuli, such as happy, sad, angry, fearful, and neutral faces. Stimuli can be presented in a variety of ways. Block, event-related, mixed, and self-driven experimental designs are commonly employed (Amaro and Barker, 2006). Analysis of task-based fMRI typically involves correlating the observed time course of BOLD signal change in each voxel with a model time course based on the expected neural response. A good fit between the two would suggest that the observed BOLD response can be attributed to the task stimulus (Brown et al., 2007).

Even in the absence of a task, there are spontaneous low-frequency fluctuations in the BOLD signal, which give rise to 'resting-state' activity within the brain (resting state functional magnetic resonance; rs-fMRI). The so-called 'resting brain' is organized into networks composed of several brain regions that have temporally correlated resting-state activity. Commonly identified networks include: visual, auditory, sensorimotor, default mode, executive control, and frontoparietal networks. The amplitude of the BOLD signal at rest is comparable with that displayed in task-related experiments (Damoiseaux et al., 2006). Furthermore, there is close correspondence between the major brain networks identified at rest and those identified during task-related fMRI experiments (Smith et al., 2009).

Two of the most widely used methods that explore how remote brain areas work together within the resting brain are independent component analysis (ICA), which examines whole networks, and single seed region analysis, which estimates the functional connectivity of a specific region (or seed) with the rest of the brain. Single seed region analyses assess the temporal correlation between the BOLD time course of a predefined seed region and that of either a priori defined target regions or the whole brain on a voxel-wise basis. Single seed region analysis can only isolate a single network based upon the predefined seed. For example, a seed in posterior cingulate cortex/precuneus is often used to investigate the default mode network, i.e. a network that is active when subjects are resting in the scanner and not engaged in a task (Fig. 12.2).

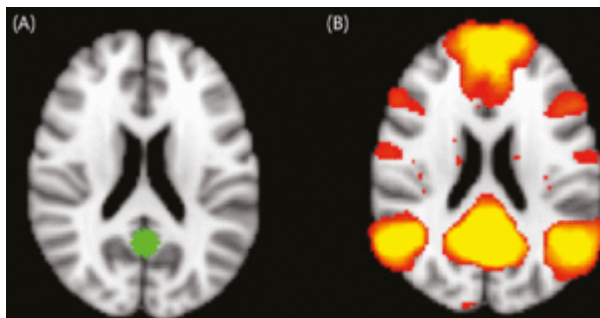


Fig. 12.2

Seed-based analysis of the posterior cingulate cortex. The blood oxygen level dependent (BOLD) signal time course of a small seed placed in the posterior cingulate cortex (A) is correlated with that of the default mode network (B). Images derived from resting-state fMRI scans in the Whitehall II Imaging sub-study.

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ICA, in contrast, decomposes the whole dataset into a set of statistically independent spatial component maps and associated time courses without a pre-specified model. Voxel values reflect the correlation between the voxel's time series and the mean time series of that particular network (Beckmann and Smith, 2004; Beckmann et al., 2005). As with other data reduction component analyses, the spatial pattern of networks generated using ICA varies according to the dimensionality, i.e. the number of components to be investigated. Low-dimensionality ICA can detect and separate several whole networks at once. Moreover, if ICA is performed for each participant separately, it can be difficult to identify the same network consistently across participants. An alternative approach is to perform ICA across all participants, and then, based upon the group-level components identified, generate individualized networks using both spatial and temporal regression (Filippini et al., 2009; Zuo et al., 2010). Networks identified in this fashion are remarkably robust across thousands of resting scans (Smith et al., 2009) (Fig. 12.3).

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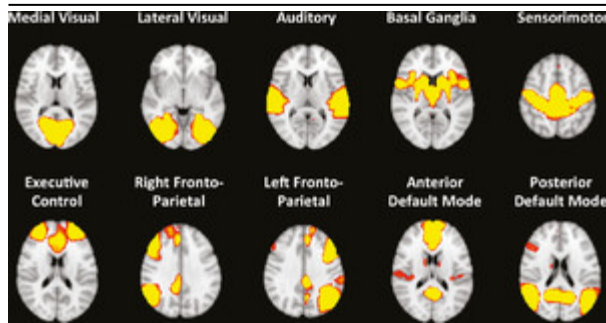


Fig. 12.3

Resting-state networks derived from low-dimensionality independent component analysis (ICA) of 500 resting-state fMRI scans from the Whitehall II Imaging Sub-study. These networks represent auditory, sensorimotor, and visual activity (top row), as well as higher cognitive processes like memory, introspection, and executive function (bottom row).

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Both single seed and whole network analyses have provided valuable insights into the organization of the brain at rest, but they are limited in their scope. Seed analyses provide information about the connectivity of a small, selected region, but are vulnerable to seed-selection biases. On the other hand, studying whole networks, each represented by a single time-course, restricts our understanding of whether and how the individual brain regions that make up the networks may be affected by outcome measures like age, cognition, or disease state. Recently emerging 'connectomics'-based approaches use graph-theory or high-dimensionality ICA to expand on traditional single seed or single network analyses and study intra- and internetwork connections across in more detail (Cole et al., 2010; Smith et al., 2013). Such network modelling methods map the 'functional connectome' by splitting the resting state fMRI scans into a large number of small distinct brain regions (nodes) and estimating the functional connectivity (edges) as the temporal correlations of node activity. Variations of the 'nodes & edges' method have been adopted to examine brain-behaviour interactions in big data neuroimaging studies like the Whitehall-II Imaging sub-study (Suri et al., 2017), the Human Connectome Project (Smith et al., 2013) and UK Biobank (Elliott et al., 2017) (Fig. 12.4).

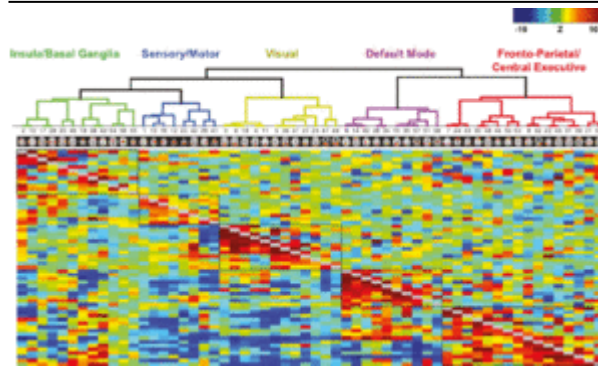


Fig. 12.4

Functional connectome derived from high-dimensionality independent component analysis (ICA) and network modelling performed on 500 resting-state fMRI scans from the Whitehall II Imaging Sub-study. The nodes and edges approach was used to parcellate the brain into 58 distinct spatial nodes (top row) and compute the correlations in time courses between the nodes (matrix). Warmer colours in the matrix represent strong positive correlations and cooler colours represent strong negative correlations in BOLD time courses between the respective nodes. The nodes are reordered according to a hierarchical clustering and are organized into five large-scale resting networks that correspond with the networks typically observed using low-dimensionality ICA.

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Blood flow MRI (arterial spin labelling)

The BOLD signal provides an indirect measure of brain function by relating the level of oxygenation in the blood of a given brain region to neural activity within that region. While it assumes that neural activity demands an increase in local blood flow, the BOLD signal does not provide a *quantifiable* measure of this increased blood flow. The most commonly used MR techniques to image perfusion, that is, the rate at which nutrient-supplying blood passes through neural tissue, are dynamic susceptibility contrast MRI (DSC-MRI) and arterial spin labelling (ASL).

DSC-MRI is a relatively quick technique that uses gadolinium (Gd) as an exogenous contrast agent in order to provide several haemodynamic measures. For example, the signal-time curve generated from the passage of the Gd-bolus through tissue can be used to calculate measures of cerebral blood volume, mean transit time, and cerebral blood flow. However, there are relative contraindications for Gd injection, including

renal failure (stage 4 or 5; GFR < 30ml/min per 1.73m²), where there is a dose-dependent risk of nephrogenic systemic fibrosis, and only a limited number of Gd injections are permissible.

In contrast, ASL uses magnetically labelled water molecules in the blood as an endogenous contrast agent to provide a measure of cerebral blood flow. In this method, arterial blood water flowing up to the brain is magnetically tagged with a brief pulse while it is still in the neck. Thus, the protons in blood destined for the brain are now inverted, making it possible to trace their path through the cerebral vasculature. An image of the brain is then acquired after a brief time delay during which the labelled blood flows from the neck into the brain. This image, called the tag image, is subtracted from a control image, in which inflowing blood is not labelled. The difference between control and tag images yields maps of cerebral blood flow, expressed in units of ml per 100 g of tissue per min. The rapid evolution of ASL methodology in the last decade has facilitated the collection of highly accurate perfusion measurements with improved signal-to-noise, which are already seeing clinical applications in acute stroke and vascular dementia (VD). Promising new ASL sequences that can measure venous oxygenation and identify selective perfusion contributions from individual arteries feeding the brain have been developed, but require further technical optimization before being translated into the clinical domain (Wong, 2013).

Diffusion tensor imaging

DTI is an MRI technique that can identify the main orientation of white matter tracts and determine their integrity in vivo. DTI is sensitive to the directional diffusion of water within neural tissues. Water molecules diffuse differently depending on the type and structural integrity of the tissue, and on their interaction with barriers like cell membranes, which restrict diffusion. For instance, diffusion in CSF is unrestricted in all directions (i.e. isotropic), whereas that in white matter is unrestricted in directions parallel to the axon but hindered orthogonally due to the presence of the myelin sheath and other longitudinal axonal structures (i.e. anisotropic) (Beaulieu, 2002) (Fig. 12.5).

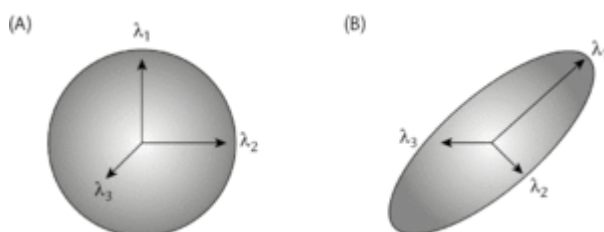


Fig. 12.5

Diffusion ellipsoids. In panel (A) isotropic diffusion is modelled as a sphere. In panel (b) anisotropic diffusion is modelled as an ellipsoid.

In diffusion-weighted imaging, the magnitude and direction of water diffusion in each voxel is measured in the x-, y- and z-dimensions. The three dimensions of diffusion can be modelled as an ellipsoid, whose shape is characterized by the three eigenvalues (λ_1 , λ_2 , λ_3). If diffusion is isotropic, diffusion in all three main axes is equal ($\lambda_1 = \lambda_2 = \lambda_3$) and the diffusion ellipsoid becomes a sphere. If diffusion is anisotropic ($\lambda_1 > \lambda_2$, λ_3), the major eigenvector reflects the direction of maximum diffusivity, which, in turn, is assumed to reflect the orientation of fibre tracts (axial diffusivity, Fig. 12.6). DTI can therefore be used to study the orientation and integrity of white matter tracts by deriving metrics that estimate the overall *direction* of diffusion (fractional anisotropy, FA), the overall *magnitude* of diffusivity (mean diffusivity, MD; apparent diffusion coefficient), axial diffusivity (diffusivity parallel to the white matter tract), and radial diffusivity (diffusivity perpendicular to the white matter tract). Such measurements can be extracted locally in previously defined ROI analysis or by tractography, or they can be measured globally, using VBA or tract-based spatial statistics (TBSS); the detail of these approaches is described below. FA and MD are considered sensitive measures of disease-related changes in white matter; axon degeneration and myelin damage are typically characterized by an increase in MD and a decrease in FA.

Measure	Formula
Fractional anisotropy	$\frac{\sqrt{1}{\sqrt{2}} \sqrt{\frac{[(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2]}{(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}}$
Mean diffusivity	$\frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$
Axial diffusivity	λ_1
Radial diffusivity	$\frac{\lambda_2 + \lambda_3}{2}$

Fig. 12.6
Formulae for DTI measures.

ROI analyses are used to examine small predefined portions of white matter tracts, and are insensitive to differences occurring outside of the ROI. *Tractography* can be used to reconstruct entire white matter tracts by predefining a starting point and automatically moving from voxel to voxel via the major direction of diffusion. However, the possibility of type II (false negative) errors remain (Mori and van Zijl, 2002) meaning some white matter tracts can be missed. *Voxel-based analysis (VBA)* involves spatial registration of each scan to a common space and performing a voxel-by-voxel whole-brain statistical comparison of white matter between groups. While VBA can provide a global assessment of white matter, it is limited by the quality of between-participant image registration (Smith et al., 2006). *TBSS* projects all participants' FA data onto an average FA tract skeleton before applying voxelwise statistics. TBSS minimizes the effects of between-participant misalignment and is more robust and sensitive than VBA (Smith et al., 2007). However, as the TBSS skeleton

consists of peak (i.e. most normal) FA values, assumed to be at the centre of the tract, TBSS may be insensitive to differences that are not uniform throughout the width of the tract, leading to conservative results.

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is an MRI technique used to quantify levels of metabolites in localized brain regions and can be used together with structural MRI to diagnose and track disease progress. For instance, while structural MRI can provide anatomical information about the size and location of a brain tumour, MRS can expand on its underlying biochemical profile.

Data from MRS are not illustrated as an image but as a frequency spectrum. The spectrum is a collection of peaks, each corresponding to a specific metabolite, and it serves as a biochemical fingerprint of the tissue; it can vary depending on the region of the brain studied, and if there is any structural damage to that region. The MR spectrum is a two-dimensional plot of metabolite frequency in parts per million (horizontal axis) versus its signal intensity (vertical axis). The exact frequency of a particular metabolite depends on its molecular structure, i.e. the number and positioning of the hydrogen atoms within the molecule (Fig. 12.7). However, because water is the most abundant hydrogen-containing molecule within tissues, its signal in the ^1H -MRS spectrum is several orders of magnitude higher than that of other metabolites (ratio of water to metabolite: 10000: 1). In order to be able to resolve weaker metabolite signals, the signal from water must be suppressed when the metabolite spectra are being acquired. This is achieved by using a water-suppressing pulse sequence during the MRS scan. MRS measurements are typically obtained in single ROI (often quite large such as several cm^3 voxels), or across a slice of the brain, but it is also possible to employ MRS across the whole brain, although this is time-consuming to do.

The most frequently employed MRS methods within old age psychiatry research are based on proton MRS (^1H -MRS) and phosphorous MRS (^{31}P -MRS). Metabolites studied using ^1H -MRS include N-acetyl aspartate (NAA), a marker of neuronal integrity; choline (Cho) (which includes free choline, phosphocholine, and glycerophosphocholine), a marker of membrane integrity and myelination; myoinositol (MI), a marker of glial integrity; and the neurotransmitters glutamate and glutamine (Glx).

Metabolites studied using ^{31}P -MRS include phosphomonoester (PME) and phosphodiester (PDE), markers of the synthesis and breakdown of membrane phospholipids, respectively; α -, β -, and γ -nucleoside triphosphate (NTP), markers of ATP; phosphocreatine (PCr), which acts as a buffer of ATP; and inorganic phosphate (Pi), which can be used to estimate intracellular pH.

As there are several experimental factors that can influence the signal amplitude, for example, the type of MRI scanner system and the brain

location being evaluated, metabolite concentration is normally measured with respect to a reference signal of known concentration, in most cases water or creatine (Cre), a marker of total cellular creatine stores and thus is often expressed as a ratio.

Emission computed tomography

Single photon emission computed tomography (SPECT)

SPECT exploits the fact that high energy radiation (γ -radiation), like X-rays, penetrates human tissue, so that the three-dimensional distribution of a molecule labelled with a γ -emitter can be reconstructed from the activity maps recorded from outside the head. Gamma-radiation is measured with γ -cameras that translate γ -photons, via scintillation counters and crystals, into electrical signals, which can then be amplified and analysed in a quantitative fashion. The 'direction of view' of the camera is determined by collimators, which admit photons only from a specific direction (see Fig. 12.8a).

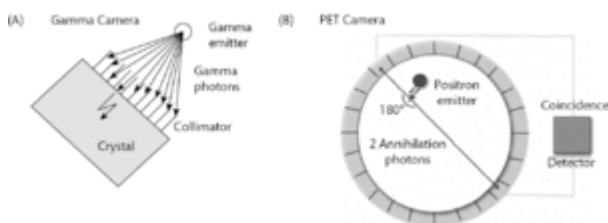


Fig. 12.8

Methods of determining site of radiation in SPECT (A) and PET (b).

However much of the radiation is absorbed within the collimator's walls, thereby reducing the sensitivity of SPECT (compare with positron emission tomography (PET); see next section and Fig. 12.8b). Common nuclei used for labelling are iodine-123 and technetium-99m. Both generate γ -radiation, with a half-life of 13.2 h (^{123}I) and 6 h ($^{99\text{m}}\text{Tc}$), respectively. Particularly ^{123}I , therefore, allows for synthesis of the tracer in a commercial laboratory and transport to the scanner. While $^{99\text{m}}\text{Tc}$ is widely generated and available locally, its use is only practicable if the labelling can be done without special skills and radio-chemical equipment, quickly, and to a high standard, as for example with $^{99\text{m}}\text{Tc}$ -HMPAO ($^{99\text{m}}\text{Tc}$ -hexamethylpropyleneamine oxime), where both components ($^{99\text{m}}\text{Tc}$ and HMPAO) are simply mixed in a vial.

A variety of biologically relevant molecules have been employed in brain imaging with SPECT, from lipophilic compounds that mark cerebral perfusion (e.g. $^{99\text{m}}\text{Tc}$ -HMPAO; $^{99\text{m}}\text{Tc}$ -ethylcysteinate dimer = $^{99\text{m}}\text{Tc}$ -ECD; n-isopropyl- ^{123}I -P- iodoamphetamine = ^{123}I -IMP) to those which radiolabel receptor ligands, for example dopamine-, serotonin-, muscarinic-, nicotinic-, and transporter-binding sites (Table 12.1). Of practical clinical importance today are some of the SPECT perfusion markers ($^{99\text{m}}\text{Tc}$ -

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HMPAO and ^{99m}Tc -ECD) mentioned in this section, and the dopamine transporter ligand ^{123}I -labelled N-(3-fluoropropyl)-2 β -carbomethoxy-3 β -(4-iodophenyl) nortropane (FP-CIT).

Table 12.1 Biologically relevant molecules used in SPECT and PET studies.

Tracer	Isotope-imaging mode	Clinical use	Measure
ECD	^{99m}Tc -SPECT	Yes	Perfusion
HMPAO	^{99m}Tc -SPECT	Yes	Perfusion
5-I-A-85380	^{123}I -SPECT	No	Nicotinic receptor
FP-CIT	^{123}I -SPECT	Yes	Dopamine transporter
Iodobenzamide	^{123}I -SPECT	No	Dopamine D ₂ receptor
Iodo-QNB	^{123}I -SPECT	No	Muscarinic receptor
Iomazenil	^{123}I -SPECT	No	Benzodiazepine receptor
FDG	^{18}F -PET	Yes	Glucose uptake (aerobic + anaerobic)
Glucose	^{11}C -PET	No	Glucose uptake (aerobic)
Oxygen	^{15}O -PET	No	Oxygen uptake
Water	^{15}O -PET	Yes	Blood flow
MP4A	^{11}C -PET	No	AChE activity
Nicotine	^{11}C -PET	No	Nicotinic receptor

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Pittsburgh compound B (PiB)	^{11}C -PET	No	Insoluble fibrillary amyloid (A β plaques)
Florbetaben	^{18}F -PET	Yes	A β plaques
Florbetapir	^{18}F -PET	Yes	A β plaques
Flutemetamol	^{18}F -PET	Yes	A β plaques
FDDNP	^{18}F -PET	No	Neurofibrillary Tangles (NFTs) and A β plaques
THK5117 and THK5351	^{18}F -PET	No	NFTs
Flortaucipir (AV-1451)	^{18}F -PET	No	NFTs
PBB3	^{11}C -PET	No	NFTs
(R)-PK11195	^{11}C -PET	No	Microglia (inflammation)
FEDAA1106 and DPA714	^{18}F -PET	No	Microglia (inflammation)
Altanserin	^{18}F -PET	No	5-HT $_2\text{A}$ receptor
WAY-100635	^{18}F -PET	No	5-HT $_{1\text{A}}$ receptor

(R)-PK11195: 1-[2-chlorophenyl]-N-methyl-N-[1-methyl-propyl]-3-isoquinoline carboxamide; 5-I-A-85380: [(123)I]-5-iodo-3-[2(S)-azetidinylmethoxy]pyridine; DPA714: N,N-diethyl-2-[4-(2-fluoroethoxy)phenyl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-acetamide; ECD: Ethylcysteinyl dimer; FDDNP: 2-(1-{6-[(2-[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl}-ethylidene)malononitrile; FDG: Fluorodeoxyglucose; FEDAA1106: N-(5-fluoro-2-phenoxyphenyl)-N-(2-[(18)F]fluoroethyl-5-methoxybenzyl)acetamide; FP-CIT: N-(3-fluoropropyl)-2 β -carbomethoxy-3 β -(4-iodophenyl) nortropane; HMPAO: Hexamethylpropyleneamine oxime; Iodo-QNB: Iodo-quinuclidinylbenzilate; MP4A: N-[(11)C]methylpiperidin-4-yl acetate; PET: Positron emission tomography; PiB: Pittsburgh Compound B;

SPECT: *Single photon emission computed tomography*; THK5117: 6-(3-¹⁸Fluoro-2-hydroxypropoxy)-2-(4-methylaminophenyl)quinoline; THK5351: (S)-6-(3-¹⁸Fluoro-2-hydroxypropoxy)-2-(N-methyl-2-aminopyridin-5-yl)quinoline; WAY-100635: N-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamide.

SPECT perfusion ligands are injected and taken up into brain cells on first pass. This means that once the tracer is injected, the patient can be imaged at any time afterwards, as long as the isotope is still active. An additional advantage is that the tracer remains in a pattern representing a snapshot of brain perfusion within two minutes of injection, so that any later interventions, sedation, or even anaesthetic do not change the image and can be used to optimize the quality of the scan.

Positron emission tomography (PET)

In contrast to this, convenient positron emitters are available in the form of ¹¹C (radioactive half-life approximately 20 min), ¹⁵O (approximately 2 min), and ¹⁸F (approximately 110 min), all substituted for the equivalent nonradioactive isotope. The short half-life implies that any synthesis of labelled tracer has to be done in-house, which increases the price of such ligands to a level that can only be afforded in specialist centres. In addition to this, the short half-life of positron emitters such as ¹¹C and ¹⁵O requires the tracer injection to be done in the scanner, which makes the procedure potentially difficult for certain patient groups.

Exceptions to this are ¹⁸F-fluoro-deoxyglucose and ¹⁸F-labelled amyloid ligands (Herholz and Ebmeier, 2011), which can be imported from within a few hundred kilometres and are injected well before the imaging session. For this reason, we will limit our discussion to such potentially clinically useful substances, although there are rapid advances in the development of novel PET tracers providing powerful insights into brain mechanisms and pharmacology in both health and disease.

The central concept in PET is that positrons emitted from the radioisotopes are annihilated within seconds and millimetres of their origin, and generate two photons of defined energy that travel in opposite directions. An instrument that can detect such coincident photons is able to locate their source on the line between the activated detectors (Fig. **12.8b**). Any photon that is not matched by a coincident partner or is of a lower energy than the predicted one is likely to be due to scatter and can be ignored. Thus, PET is generally more sensitive than SPECT, where, in the latter, much of the potentially available radiation is absorbed by the collimator walls.

In common with SPECT is the exposure to radioactive isotopes, which may be trivial in the single case, but adds to the overall population exposure to ionizing radiation. For this reason, BOLD fMRI and arterial spin labelling MRI have taken over virtually all experimental research

applications of ^{15}O -water PET for blood flow. An exception is ^{18}F -FDG PET in dementia research, where the logistics of scanning (injection at rest 30–45 minutes before the scan), its availability in oncology/specialist centres, its quantitative nature, and the age group of the patients involved (where radiation risk is minimized) make it the preferred method of imaging current brain function (Herholz et al., 2002). In addition, ^{18}F -FDG PET provides a more direct ‘window’ on brain function as it measures brain metabolism rather than perfusion.

Abnormal aggregation of amyloid plaques and hyperphosphorylated tau are the hallmarks of Alzheimer’s disease (AD) pathology. It is, therefore, not surprising that efforts have been made to label amyloid and more recently, to characterize tau in vivo (Saint-Aubert et al., 2017; Herholz and Ebmeier, 2011). As amyloid deposition is found in healthy older people’s brains especially over the age of 80, the diagnostic accuracy of amyloid PET scanning for AD in this group is limited. Current efforts focus on the predictive validity of increased amyloid binding in mild cognitive impairment (MCI), as some people in this diagnostic category have normal scans, and others have abnormal amyloid scans. A potential shortcoming of the ligands in development is non-specific white matter binding, but this may be overcome in practice (Herholz and Ebmeier, 2011). If future therapeutic agents were to remove amyloid deposits, an in vivo amyloid ligand would provide a way to monitor treatment success directly.

Unlike amyloid, tau deposits are present intracellularly, and until recently these pathological lesions could only be studied using immunohistochemistry in post-mortem brain tissue.

Over the last five years, there has been an emergence of promising tau-specific PET tracers to study the spatial patterns of tau deposition in AD and other tauopathies, and monitor the spread of tau during disease progression (Saint-Aubert et al., 2017; Bischof et al., 2017). However, currently, a number of caveats have to be considered. In vitro, the available tracers have shown different affinities towards subtypes of tau. ^{18}F -AV-1451 demonstrated stronger binding to combined 3+4 repeat tau (characteristic of AD) compared to exclusive 3-repeat (e.g. behavioural variant-FTD) or 4-repeat tau, such as corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP). When directly compared to ^{18}F -AV-1451, the tracer ^{11}C -PBB3 showed stronger binding to tau aggregates in 3-repeat and 4-repeat pathologies (Ono et al., 2017).

In addition, tau tracers have demonstrated non-specific binding (e.g. to neuromelanin), mainly to subcortical structures, especially in the striatum and in the choroid plexus. Of particular concern is the fact that some of the regions showing off-target binding in vivo are regions where specific binding would be expected in some tauopathies, e.g. the basal ganglia in CBD and PSP. The available tau tracers have differential properties to off-target binding, limiting their comparability. Further standardization of the tracers is required before tau PET can be used as a biomarker; their

potential in the differential diagnosis of different tauopathies is discussed in more detail further on.

PET molecular imaging techniques are also used to study inflammation in neurodegeneration. The great majority of these ligands target the overexpression of the 18-kDa translocator protein (TSPO). TSPO is an outer mitochondrial membrane translocator protein, expressed mostly by microglia. Its levels in the brain of healthy controls are low, while they rise in neurodegenerative diseases. ^{11}C -(R)-PK11195 is the first and best validated TSPO ligand. Second-generation ligands have been subsequently introduced, but it was found that a single-nucleotide polymorphism (rs6971) in the TSPO gene can significantly influence their uptake, making genetic testing mandatory for research studies using this ligand. Other limitations of TSPO as PET imaging molecular target exist, such as multicellular expression, low brain density even in disease states, similar expression in microglia regardless of its phenotype (pro-inflammatory or anti-inflammatory), as well as lack of a specific brain region of negative control (Tronel et al., 2017). Alternative targets are under evaluation. They include receptors (purinergic P2X7, cannabinoid CB2R, adenosine 2A) and enzymes (cyclooxygenase, nitric oxide synthase, matrix metalloproteinases), with a particular focus on their selectivity for microglial expression and polarization (Tronel et al., 2017).

Electromagnetic fields

Electroencephalography

Electroencephalography (EEG) is a non-invasive functional technique that records electrical fields along the scalp using electrodes placed in a cap over the head. The recorded electric potentials are generated by populations of thousands of neurons that have a similar orientation and fire synchronously. The pyramidal neurons of the cortex have these properties and therefore their activity is thought to underlie EEG signals. While the temporal resolution is much higher compared with fMRI—signals can be recorded only milliseconds after the presentation of a stimulus—the spatial resolution is greatly reduced (Fig. 12.9). One reason is that the strength of the electric potential that is measured by EEG falls off with the square of the distance, which impairs the detection of subcortical neuronal activity. Additionally, the skull and scalp cause distortions of the signal, which makes exact localization of neural activity difficult.

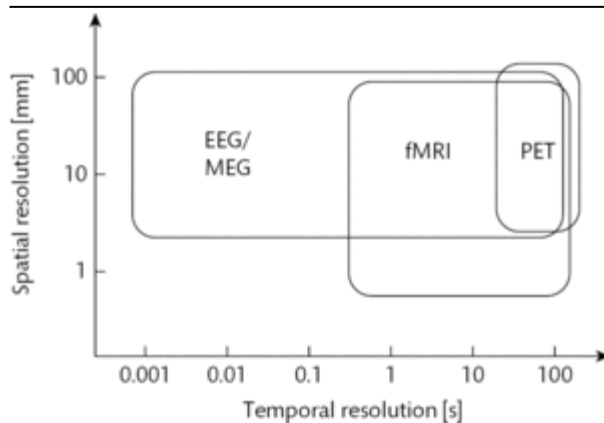


Fig. 12.9
Spatial and temporal resolution of different neuroimaging techniques.

Magnetoencephalography

In contrast to EEG, magnetoencephalography (MEG) is used to measure magnetic fields that are induced by the electric activity of neurons. These magnetic fields are measured using superconducting quantum interference devices (SQUIDs) as sensors that are arranged in a helmet placed over the head.

A disadvantage of MEG is that it can only record signals from neuronal pathways that run in parallel to the skull. Therefore, the main contribution to MEG signals comes from neurons located within cortical sulci and deeper sources of activity are less visible to MEG. However, the advantage of MEG is that the magnetic field is less influenced by changes of conductivity between brain, skull, and scalp, which improves localization of neuronal activity particularly, if the activity is superficial.

There are several ways of analysing EEG and MEG data. One might be interested in the electrophysiological response with respect to the onset of a specific stimulus. This response is called an event-related potential (ERP) in EEG and an event-related field (ERF) in MEG, and occurs phase-locked to stimulus onset. Averaging many synchronized EEG traces removes noise and emphasizes any regular responses to the stimulus. Similarly, EEG/MEG can be phase-locked to the subject's response, if the main interest is in processes leading up to a motor response. It is alternatively possible to study changes in the power of oscillations in electric activity in specific frequency bands. More synchronized neuronal firing is thought to underlie increased power of oscillations. Typical frequency bands of interest are delta (less than 4 Hz), theta (4–7 Hz), alpha (8–13 Hz), beta (14–30 Hz), and gamma (30–100 Hz). The power of oscillations can be measured with respect to a stimulus onset (induced activity), which is called event-related synchronization (ERS) or desynchronization (ERD). It can also be measured independently of a

stimulus (spontaneous activity) when subjects are resting during the measurement and not engaged in a specific task.

Several techniques can be used to reconstruct the source of neuronal activity, e.g. equivalent current dipole modelling and beam-former approaches. All of these techniques use specific constraints to locate neuronal activity because theoretically there are an infinite number of solutions to explain the MEG/EEG signal. This is known as the inverse problem.

Clinical Applications

What is involved for the patient?

A structural MRI scan with sequences sensitive to pathological changes typically lasts less than 30 minutes, but in research settings, multimodal MRI acquisition can take up to one hour. A major limitation to scan length is participant comfort and compliance, which also has an effect on image quality (e.g. movement artefacts). There are a number of contraindications to MRI, including pacemakers, certain metallic implants, and severe claustrophobia. CT has several advantages over MRI as it is cheap, widely available, and often suitable for patients with contraindications to MRI. While MRI typically requires lying in a narrow scanner, the more open design of CT, and also of emission tomography scanners, makes them more acceptable for some patients. However, most research is now conducted using MRI techniques as it provides higher resolution images, greater soft tissue contrast, and does not involve ionizing radiation.

PET and SPECT scans are used in various centres, according to their availability. With a trend for PET to become more widely available, PET-CT scanners are being acquired by many services for oncological examinations, although their availability for psychiatric patients is likely to remain limited. Both PET and SPECT are likely to fulfil the requirements of diagnosis and differential diagnosis and can be used interchangeably (Ebmeier, 2010), except in cases where appropriate ligands are not available in a modality (e.g. dopamine transporter ligands are not commercially available for PET, and amyloid ligands for SPECT are not on the horizon). Both scan modalities are relatively user friendly, with an open gantry and little noise. Their main limitation is the radiation dose administered parenterally, both in terms of the necessity of an injection and the (usually very small) risk to the patient from ionizing radiation.

EEG and ERPs are no longer commonly used in clinical psychiatric practice, except in the differential diagnosis of epilepsy and multiple sclerosis, although they have several advantages compared with MRI. EEG equipment is user friendly, cheaper, and more mobile, and recordings do not require a strong magnetic field. Patients merely have to sit still, or engage in simple tasks, usually attentional auditory or visual

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tasks. Nevertheless, analysis of EEG data is not straightforward, requires special neurophysiological skills, and is strongly affected by current mental state and by medication, which may be one explanation why it is not generally used in the clinic. Computational and advanced analytics are helping improve the diagnostic specificity of EEG in terms of dementia diagnosis, but these approaches still remain primarily within research domain (see Potential diagnostic use).

MEG is not generally available and is predominantly used for research, where it is well tolerated even by the very young and old, as well as cognitively impaired patients.

Making a diagnosis

Current clinical practice

CT and MRI are commonly used in the evaluation of patients with cognitive impairment and other psychiatric syndromes (see Table 12.2). CT is used in the diagnosis of stroke (haemorrhagic or old ischaemic), large tumours, intra- and extracranial bleeding, atrophy, (communicating) hydrocephalus, and trauma. MRI is preferred for the investigation of conditions only detectable with higher resolution and greater soft tissue contrast, such as temporal lobe epilepsy (medial temporal gliosis), multiple sclerosis, certain tumours (e.g. pituitary adenomas), and certain vascular changes.

Table 12.2 Magnetic Resonance Imaging (MRI) used in the diagnostic criteria of some dementias.

Disease	Diagnostic criteria	MRI marker	Use
Alzheimer's dementia	NINDS-ADRDA (McKhann et al., 1984) NIA-AA (McKhann et al., 2011)	'Normal MRI' Medial temporal atrophy	Exclusion Most validated structural topographical marker
Creutzfeldt-Jacob disease	(Collie et al., 2001; Tschampa et al., 2005)	Cortical diffusion changes, pulvinar sign	Diagnostic (included in the criteria for a diagnosis of CJD)
Dementia with Lewy bodies	(McKeith, 2006;	Preserved medial temporal	Supportive*

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	McKeith et al., 2017)	lobes, relative to Alzheimer's dementia	
Frontotemporal degeneration	(Neary et al., 1998; Rascovsky et al., 2011; Gorno-Tempini et al., 2011)	Focal frontal or temporal atrophy	Supportive*
Multiple system atrophy	(Gilman et al., 2008)	Atrophy of putamen, middle cerebellar peduncle, pons, and/or cerebellum	Supportive*
Progressive supranuclear palsy	(Boxer et al., 2017)	Atrophy of midbrain, 'hummingbird sign'	Supportive*
Vascular dementia	NINDS-AIREN (Roman et al., 1993)	Strategic infarction, extensive white matter changes	Mandatory**
CADASIL	(Zhu and Nahas, 2016)	Confluent white matter hyperintensities, lacunar infarcts, involvement of the anterior temporal lobes	Mandatory**

*Supportive features: consistent with the diagnosis, but without clear diagnostic specificity;

**Mandatory features: required for a diagnosis; NINDS-ARDA: National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; NINDS-AIREN: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; CJD: Creutzfeldt-Jakob Disease; CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Although the exclusion of surgical or non-degenerative causes of cognitive impairment remains an important justification for imaging, there is an increasing focus on identifying biomarkers that help to support a clinical diagnosis of the underlying cause of the dementia. While no imaging feature has perfect sensitivity and specificity for any given diagnosis, there are a number that help to narrow the differential diagnosis. Further validation of these biomarkers is required before they can be implemented in routine clinical practice.

Potential diagnostic use

Dementia of Alzheimer type (AD)

The MRI technique that is arguably closest to translation to the clinic is T₁-weighted MRI in the diagnosis of AD (Dubois et al., 2010; McKhann et al., 2011). A key feature of AD is early, localized atrophy of the medial temporal lobe (MTL), including the hippocampus and entorhinal cortex (Fig. 12.10), which is followed by generalized neocortical volume loss. Hippocampal atrophy is thought to occur early, and three years prior to diagnosis hippocampal volumes are already reduced by 10% (Johnson et al., 2012). T₁-weighted MRI is an ideal tool to examine such patterns of atrophy in vivo, with volumetric measures found to correlate well with both neuropathological disease progression (Gosche et al., 2002; Jack et al., 2002; Vemuri et al., 2008), and the degree of cognitive impairment (Hua et al., 2008; Vemuri et al., 2009). Moreover, T₁-weighted MRI studies of AD have progressed from reporting case-control group differences to automatic classification of individual scans. A multisite study involving 98 AD and 109 control participants obtained a specificity rate of 95% (controls correctly identified as controls, i.e. correct negative rate) and a sensitivity rate of 71% (patients correctly identified as patients, i.e. correct positive rate) (Vemuri et al., 2009). Smaller studies have also reported success in discriminating between AD and other dementias (Kloppel et al., 2008).

Medial temporal atrophy (MTA) is highly sensitive for AD and has been incorporated into diagnostic criteria as a topographical marker of downstream neuronal injury (Dubois et al., 2010; McKhann et al., 2011). However, MTA is found in other dementia subtypes, e.g. frontotemporal dementia (FTD) and VD (Johnson et al., 2012), and its specificity decreases with age due to age-related atrophy (van de Pol et al., 2006). In atypical or early-onset AD it is possible to have greater atrophy of the parietal lobes and less MTA (Galton et al., 2000; Frisoni et al., 2007; Karas et al., 2007).

Other structural neuroimaging markers of AD have not yet been tested in large-scale classification studies, but may have potential to reach that stage. AD has traditionally been conceptualized as a disorder of the grey matter, and white matter damage has been thought to occur secondary to grey matter atrophy. It has now been suggested that white matter damage occurs independently of, and perhaps even before, grey matter

damage (Suri et al., 2014). For example, DTI studies of AD have typically detected a pattern of decreased FA and increased MD values in AD compared with controls. A meta-analysis of 33 case-control studies of AD found that AD was associated with reduced FA and elevated MD values in widespread regions, including within frontal and temporal white matter, the posterior cingulum, corpus callosum, superior longitudinal fasciculus, and uncinate fasciculus (Sexton et al., 2011). Furthermore, several studies have reported a significant association between decreased MMSE in AD and reduced FA, or increased MD (Bozzali et al., 2002; Duan et al., 2006), indicating that DTI metrics may be sensitive markers of disease progression. A meta-analysis demonstrated that DTI measurements of limbic regions yielded moderate to large effect sizes (Hedge's g 0.73–0.97) that were similar to those of hippocampus atrophy (Hedge's g 0.61–1.98), when discriminating between controls and patients with AD or MCI (Clerx et al., 2012).

Rs-fMRI studies in AD have shown that disconnection of the default mode network happens early in the disease course (Barkhof et al., 2014), but evidence from larger studies is required to confirm this. There is an extensive literature on regional cerebral blood flow and regional glucose metabolism studies in dementia (Ebmeier, 2010; Herholz, 2011), so that recent proposals for diagnostic criteria for AD suggest ^{18}F -FDG-PET as a topographical diagnostic marker (Dubois et al., 2010; McKhann et al., 2011). Notably, functional changes precede atrophy detectable by structural imaging. The characteristic AD patterns of abnormal brain perfusion or metabolism are found in the association cortex, while primary sensory-motor cortex is relatively preserved (Ebmeier, 2010), with a ratio of association cortex activity over primary sensory-motor cortex activity being suggested as a diagnostic index for AD (Herholz et al., 1999). Early in the disease course, SPECT and FDG-PET show reduction in posterior cingulate and precuneus perfusion or metabolism, followed by bilateral posterior temporoparietal reductions and involvement of the frontal areas in advanced disease (Mosconi et al., 2008; Ebmeier, 2010; Herholz, 2011). The findings in functional scans correlate with CSF biomarkers (Ceravolo et al., 2008), as well as with cognitive measures (Arlt et al., 2009). PET is more sensitive than clinical assessment in detecting AD (90% vs 81%), while both SPECT and PET are more specific than AD clinical criteria (85% and 89% vs 70%) (McKhann et al., 2011).

In addition, the use of amyloid tracer uptake has been suggested as a pathophysiological marker of AD (McKhann et al., 2011), although there are a number of caveats extending from the lack of availability of ^{11}C -labelled compounds (Pittsburgh compound B, PiB) to the relative lack of specificity of the available ligands which can show abnormalities in both MCI and healthy volunteers (Herholz and Ebmeier, 2011) (Fig. 12.11). There are, however a number of ^{18}F -labelled tracers (flutemetamol, florbetapir, and florbetaben) that will at least make amyloid imaging

available away from specialist radiochemistry laboratories (Herholz and Ebmeier, 2011).

Amyloid imaging provides direct evidence of the presence of Alzheimer's type pathology with A β plaques markers becoming positive years before clinical symptoms and reaching a plateau by the time clinical symptoms appear (Jack et al., 2010). Amyloid PET tracers bind with high affinity to fibrillary amyloid. More than 90% of patients with AD show increased cortical binding (Rabinovici and Jagust, 2009) and false-negative cases are reported only rarely (Cairns et al., 2009). Up to 35% of cognitively normal older people, however, have positive amyloid-PET results, and therefore amyloid imaging has low positive predictive value (Rice and Bisdas, 2017). The relative frequency of positive amyloid scans increases with age and is higher in ApoE4 carriers, compared to non-carriers, as well as in people with maternal familial history of AD (Morris et al., 2010; Rowe et al., 2010; Mosconi et al., 2010).

Amyloid imaging is useful in differentiating AD from non-amyloid dementias such as FTD (Rabinovici et al., 2011; Rowe et al., 2007), particularly in early-onset dementia, when the prevalence of AD equals to that of FTD and the frequency of amyloid deposition in controls is low. There is no uptake in most cases with Parkinson's disease (PD) dementia (Maetzler et al., 2008), but positive scans are common in dementia with Lewy bodies (DLB) (Rowe et al., 2007; Villemagne et al., 2011), which is consistent with pathological findings (Harding and Halliday, 2001). In patients with VD, a positive scan can confirm the presence of mixed pathology which has implications for treatment.

As noted previously, more recent advance in molecular PET imaging is the evaluation of cerebral tau burden. Unlike amyloid pathologies, which do not reflect disease progression, cortical tau pathology correlates with the degree of cognitive impairment and neurodegeneration (Johnson et al., 2016; Cho et al., 2016). Tau tracer retention patterns are also consistent with the expected distribution of tau pathology according to neuropathology findings, including in atypical forms like posterior cortical atrophy and the logopenic variant of primary progressive aphasia (Warren et al., 2012). While this is an encouraging breakthrough in AD research, extensive work is still needed in this field to fully characterize the binding properties of tau PET tracers and relate it to amyloid deposition as well as disease severity.

In regard to PET in vivo measurements of neuroinflammation, several studies demonstrated an increased ¹¹C-PK11195 uptake in AD compared to controls, with the largest effect in the temporoparietal cortex (Cerami et al., 2017). Cortical microglial activation was significantly correlated with cognitive status and negatively correlated with glucose metabolism and hippocampal volumes in AD (Fan et al., 2015; Femminella et al., 2016). A longitudinal study showed an increase of microglial activation in

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the MTL over 16 months, paralleling the observed reduction in MTL volumes (Fan et al., 2015).

Positive TSPO PET has been found in other neurodegenerative diseases, including FTD, DLB, atypical parkinsonism, and in prion diseases, which supports the hypothesis that glial activation reflects a generic pathological response to neurodegeneration, rather than a specific reaction to a given toxic protein (Cerami et al., 2017).

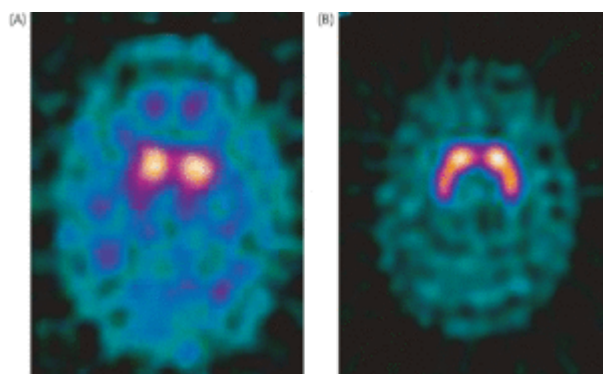


Fig. 12.12

DatScan SPECTs (dopamine transporter) of (A) dementia with Lewy bodies (note apparent greater activity across the brain, due to normalization procedure) and (b) Alzheimer's dementia.

Reproduced courtesy of Prof. John T. O'Brien and Dr Sean Colloby, Institute of Neuroscience, Newcastle University.

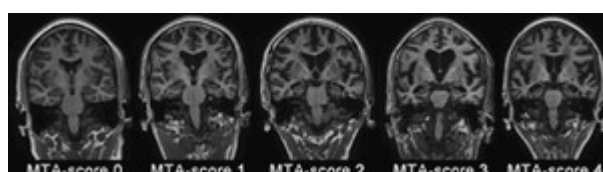


Fig. 12.10

T₁-weighted MRI scans to illustrate Scheltens scale medial temporal atrophy (MTA) scores 0-4.

Reproduced courtesy of Prof. Ph. Philip Scheltens, Alzheimer Center Amsterdam.

Although EEG has been shown to be useful in AD research for the last 30 years, there has not been a proper translation into the clinic. One reason might be that there are no large-scale studies investigating the clinical use of EEG to discriminate between AD patients and healthy controls. This is surprising given the good results of resting-state EEG studies. AD is characterized by slowing of cortical rhythms. Early stages of AD are associated with increased theta and delta band activity and decreased

beta band activity, followed by a decrease in alpha activity. Additionally, dementia severity correlates with the mean frequency of power spectra (Jeong, 2004). This could be used for diagnostic purposes. For example, a specificity rate of 83% and sensitivity of 87% was achieved comparing global amplitudes of power in the alpha and theta frequency range between 38 AD patients and 24 healthy controls (Huang et al., 2000). Differences in amplitude and latency of several ERP components have also been reported when comparing AD patients with healthy controls (Jackson and Snyder, 2008).

EEG may aid the differential diagnosis of other dementia syndromes. In sporadic CJD (sCJD) the EEG is characterized by diffuse slowing and FIRDA (frontal intermittent rhythmic delta activity) in early stages, and the typical periodic sharp wave complexes (PSWC) that develop with disease progression. Lateralized or generalized PSWC occurs in about two-thirds of patients with sCJD and has a positive predictive value of 95%; it rarely, if at all, occurs in vCJD. EEG recording is included in the World Health Organization diagnostic classification criteria for CJD (Malek et al., 2017).

In a study comparing patients with different dementia subtypes, focal abnormalities, local 'irritative' phenomena (spikes and/or sharp waves), and slow wave paroxysms were more common in patients with VD than in those with AD (Erkinjuntti et al., 1988). Another study compared patients with AD, FTD, and controls and found that in FTD, there was no increase in slow wave activity and a decrease in fast wave activities (Lindau et al., 2003). A normal EEG in a patient with a clinical diagnosis of dementia should be a cause for reconsidering the diagnosis; one possibility is (untreated) depression, in which the amount of slow wave activity is near normal (Malek et al., 2017).

Latterly, advanced EEG analysis methods have become available, e.g. functional connectivity and network analysis. Especially in the higher frequency bands, AD patients have lower functional connectivity than healthy controls. The changes in connectivity are not equally distributed across brain regions, and at the regional level, connectivity increases have been described as well. The EEG-based functional brain networks of AD patients have been found to differ from those of healthy controls, but the interpretation of the results is constrained by methodological limitations (van Straaten et al., 2014).

MEG studies in AD consistently show that MEG oscillations are slower in AD patients than in controls. A review of 31 studies concluded that, compared to controls, AD patients had slower brain activity, which was reflected in a higher power in the lower frequency bands and lower power in the higher frequency bands consistent with EEG studies in AD. The most affected brain regions were left parietal and left temporal, followed by left occipital, with the central region being less affected. In addition, brain signals in AD were more regular, less complex, and more predictable than in controls; these results are in line with the EEG

findings (Engels et al., 2017). To date, there are only a few MEG-based connectivity and network studies, but largely they support the concept of AD as a 'disconnection syndrome' (Engels et al., 2017). For instance, in a study of resting-state MEG, 22 AD patients showed reduced mean frequency of power spectra, compared with 21 healthy controls (Fernandez et al., 2006a). Further analysis of the same subject group showed that relative power in the 16- to 28-Hz frequency band can differentiate between AD patients and healthy controls with 80% specificity and 81% sensitivity, respectively (Fernandez et al., 2006b). There are only a few MEG studies in other types of dementia and they largely support the EEG findings.

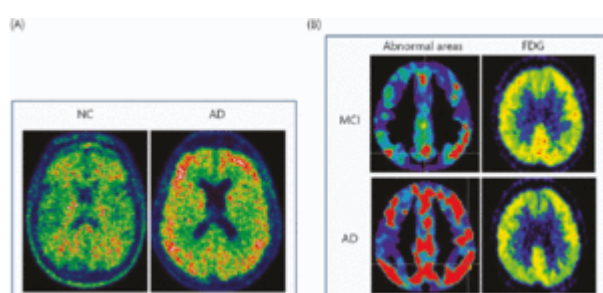


Fig. 12.11

^{18}F -FDG (^{18}F -Fludeoxyglucose) and ^{11}C -PiB (11C-Pittsburgh compound B) scans in healthy controls and patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD). (a) Amyloid scan with florbetapir in a normal control (NC) and an AD patient. Note tracer uptake in white matter of the healthy volunteer brain. (b) FDG scan in a patient with MCI and two years later, when he had progressed to AD. The left column highlights the abnormal areas in black (association cortex).

Reproduced courtesy of Prof. Karl Herholz.

Vascular dementia (VD)

Evidence from structural neuroimaging is mandatory for diagnosing VD. VD can result from large artery (cortical) ischaemic disease, small vessel (subcortical) disease (SVD), or bilateral thalamic/fornix infarcts (strategic infarcts) leading to severe memory deficits.

SVD is the most common cause of VD. It results from damage to the cerebral microcirculation and is defined as lesions involving > 25% of the white matter (Pantoni, 2010). Radiologically, SVD is characterized on MRI by WMH, recent small subcortical infarcts, lacunae, prominent perivascular spaces, cerebral microbleeds, and atrophy (Wardlaw et al., 2013) (see Table 12.3). These signs are present in up to 10% of patients in their seventh decade, increasing to above 85% of those in their ninth decade (Blair et al., 2017). They are present in healthy elderly, but are

strongly associated with vascular risk factors and cognitive impairment (Pernecky et al., 2016).

Table 12.3 Neuroimaging (MRI) features of small vessel disease.

Neuroimaging

	Recent small subcortical infarct	Lacuna	White matter hyperintensity	Perivascular space	Cerebral microbleed
Definition	Neuroimaging evidence of recent infarction in the territory of one perforating arteriole, with imaging features or clinical symptoms consistent with a lesion occurring in the previous few weeks	A subcortical, fluid-filled cavity consistent with a previous acute small subcortical infarct or haemorrhage in the territory of one perforating arteriole	Signal abnormality characterized by hyperintensity on T ₂ -weighted images without cavitation	Fluid-filled spaces that follow the typical course of a vessel as it goes through grey or white matter	Small areas of signal void with associated blooming
Best sequence	DWI	FLAIR	FLAIR	T ₁ /T ₂ /FLAIR	T ₂ */SWI
Diameter	≤ 20mm	3-15mm	variable	≤ 2mm	≤ 10mm
Comment		Round or ovoid, usually with hyperintense rim	Located in the white matter	Most linear without hyperintense rim	Round or ovoid, well defined, blooming
DWI	↑	↔/(↓)	↔	↔	↔
FLAIR	↑	↓	↑	↓	↔
T₂	↑	↑	↑	↑	↔

Neuroimaging

T₁	↓	↓	↔/ (↓)	↓	↔
T₂*-weighted GRE	↔	↔ (↓ if haemorrhage)	↑	↔	↓↓

DWI: diffusion-weighted imaging; FLAIR: fluid-attenuated inversion recovery;

SWI: *susceptibility-weighted imaging*; T₂: *weighted MRI*; T₁: *weighted MRI*;

T₂*: *weighted GRE (gradient-recalled echo)*

↑ : *increased signal* ↓ : *decreased signal* ↔ : *iso-intense signal* Adapted with permission from Wardlaw, J.M., et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. The Lancet Neurology, 12(8): 822–838. Copyright © 2013 Elsevier Ltd. All rights reserved. DOI:[https://doi.org/10.1016/S1474-4422\(13\)70124-8](https://doi.org/10.1016/S1474-4422(13)70124-8).

White matter lesions appear as bilateral, mostly symmetrical hyperintensities on T₂-weighted MRI. WMH are clinically and pathologically heterogeneous (Gouw et al., 2011; DeBette and Markus, 2010); they are not specific to VD and can be found in other conditions including leukodystrophies, leukoencephalopathies, inflammatory conditions, and infections (Harper et al., 2014). WMH in AD might be a marker for Wallerian degeneration triggered by cortical AD-pathology; in this case they have a posterior predominance (McAleese et al., 2017). Currently it is not known why some individuals are symptomatic at early stages of SVD, while others have significant radiological findings and no apparent symptoms. However, as WMH become more extensive they are more likely to be clinically significant (Dufouil et al., 2009), with confluent deep and large irregular WMH being typical of VD.

SVD shares common risk factors with large vessel atherosclerotic vascular disease, e.g. age, hypertension, hypercholesterolemia, diabetes, and smoking, but it is now understood to be a distinct, endothelial disease, likely to require different treatments than traditional plaque-targeted vascular therapies. Recent advances in imaging SVD include quantifying the total SVD burden, imaging brain microstructural integrity, and assessing vascular malfunction. These methods have the potential to identify early disease stages and tissues at risk of progression to more established brain damage. They may be used in the future to stratify patients entering trials and to identify new treatment targets (Blair et al., 2017).

Although still in development, DTI can detect subtle microstructural changes that precede brain atrophy and may be missed by volumetric methods. Using voxel-wise DTI analyses, patients with vascular cognitive impairment had significantly decreased FA in hemispheric deep white matter and corpus callosum compared to healthy controls (Otsuka et al., 2012). Research suggests that the impairment of white matter integrity is more extensive in VD than in AD. Using TBSS, Zarei and colleagues (2009) found that, relative to controls, patients with VD had more widespread reductions in FA in frontal and parietal areas, whereas patients with AD had reduced FA in the temporal lobes.

Typical findings in VD are multiple small lesions of hypoperfusion or hypometabolism, often asymmetrical in distribution, extending over cortical and subcortical structures.

Frontotemporal dementia (FTD)

Currently validated imaging biomarkers in FTD include grey matter atrophy, brain hypometabolism detected by FDG-PET, and brain hypoperfusion detected by HMPAO-SPECT.

FTD encompasses a heterogeneous group of conditions and can be broadly divided into behavioural variant frontotemporal dementia (bv-FTD) and primary progressive aphasia (PPA) (see Chapter 33 for further

elaboration). The most recently published guidelines include as a criterion for establishing a diagnosis of 'probable' FTD evidence for abnormalities on either structural or functional brain imaging in addition to a clinical diagnosis (Rascovsky et al., 2011; Gorno-Tempini et al., 2011).

Bv-FTD is associated with atrophy in the frontal and temporal lobes, the insula, and the anterior cingulate cortex, with the earliest involvement of frontal paralimbic cortices and insula (Meeter et al., 2017). Cluster analyses identify four anatomical forms of bv-FTD: frontal-dominant, temporal-dominant, frontotemporal, and distributed frontotemporoparietal (Meeter et al., 2017). With the disease progression, subcortical structures such as the hippocampus, amygdala, basal ganglia, and thalamus are involved as well (Meeter et al., 2017).

PPA is itself categorized into three clinical phenotypes: semantic variant PPA (sv-PPA), non-fluent PPA (nv-PPA), and logopenic variant PPA (lv-PPA). In sv-PPA, there is typically anteroinferior temporal lobe atrophy, including the fusiform gyrus, while the nv-PPA is characterized by perisylvian atrophy and involvement of the insula (Rohrer et al., 2009; Seelaar et al., 2011). The lv-PPA is commonly associated with Alzheimer's type pathology and the atrophy involves the posterior temporal cortex and inferior parietal lobule (Gorno-Tempini et al., 2004). In PPA the atrophy is more often asymmetrical, with the left side being more affected (Seelaar et al., 2011); with disease progression, the atrophy involves the opposite hemisphere as well. In addition to distinct patterns of regional atrophy that are associated with each clinical phenotype, the rate of atrophy was found to be doubled in FTD and semantic dementia, compared with AD (Krueger et al., 2010).

When available, functional imaging such as FDG-PET may be more useful because early in the disease course the structural scan can be normal. The patterns seen on functional imaging mirror those seen on structural scans, but they are visible earlier, sometimes a few years before patients fulfil the criteria for probable bv-FTD (Meeter et al., 2017). In patients with suspected FTD, the use of SPECT/PET increased sensitivity of consensus criteria from 36.5% to 90.5%, where clinical diagnosis after two years was used as a gold standard (Mendez et al., 2007). In primary psychiatric disorders that mimic bv-FTD, false positive FDG-PET scan results have been reported, requiring caution if this is the only abnormal investigation (Meeter et al., 2017).

New imaging biomarkers for FTD are in the process of development, but have not yet been tested in large studies. For instance, DTI studies demonstrate that changes in white matter microstructure are more widespread in FTD compared to AD, and whole brain mean FA discriminates between FTD and AD with a sensitivity of 78% and specificity of 68% (Meeter et al., 2017). The key white matter tracts involved in bv-FTD seem to be the uncinate fasciculus, cingulum bundle, and the genu of corpus callosum, although patterns of white matter

damage on DTI significantly overlap between FTD subtypes (Meeter et al., 2017).

Using ASL, hypoperfusion in the insula, the amygdala, and parts of the medial frontal lobes including the anterior cingulate was found in patients with FTD. Comparative studies demonstrated that the regions found on ASL MRI overlapped with those on FDG-PET scans, with the two modalities having similar performance for distinguishing bv-FTD from AD and controls (Verfaillie et al., 2015; Tosun et al., 2016).

The most consistent rs-fMRI finding in FTD is decreased connectivity between the frontoinsula and anterior cingulate cortex, which is a part of the salience network, although normal or increased connectivity has been reported as well (Meeter et al., 2017).

Dementia with Lewy bodies (DLB)

Reduced dopamine transporter (DAT) uptake in basal ganglia demonstrated by SPECT (FP-CIT) or PET imaging is the most reliable imaging biomarker of DLB, and has been incorporated as 'indicative' biomarker in the revised criteria for DLB (McKeith et al., 2017) (Fig. 12.10). It has also been recommended by the United Kingdom National Institute for Health and Care Excellence (NICE) if the diagnosis is uncertain and DLB is suspected (NICE, 2018).

Compared with autopsy results, DAT imaging showed sensitivity and specificity of 88% and 100%, respectively, whereas clinical diagnosis had a sensitivity of 75% and specificity of only 42% (Walker et al., 2007). Normal DAT scan in patients with DLB is not common, but has been reported; it is possible that these patients have exclusive cortical involvement with relative sparing of basal ganglia (Siepel et al., 2013) or a balanced loss across the whole striatum (McKeith et al., 2017).

DAT density is highest in striatum, i.e. caudate and putamen. Age-related nigrostriatal degeneration affects both the putamen and caudate nucleus, and the putamen-to-caudate ratio is preserved (Tatsch and Poepperl, 2013). In PD and DLB, however, there is usually a pronounced reduction in FP-CIT signal, often with greater reduction in activity in the putamen. Because antipsychotic drugs bind to the postsynaptic D₂ receptors and not DAT, drug-induced parkinsonism shows a normal uptake pattern for FP-CIT. DAT imaging is useful in the differential diagnosis of DLB from AD; its utility is well-established, with sensitivity of 78% and specificity of 90% (McKeith et al., 2017). However abnormal DAT binding is less reliable in differentiating DLB from FTD because about 30% of patients with FTD were found to have a positive DAT scan (Morgan et al., 2012). Vascular parkinsonism may show a pronounced lateral asymmetry of striatal binding, but idiopathic PD also often presents with asymmetrical FP-CIT uptake. It is important to recognize that a DAT scan cannot differentiate between other syndromes characterized by dopaminergic

loss, such as the atypical parkinsonian syndromes, e.g. PSP or multiple system atrophy, parkinsonian variant (MSA-P), or CBD.

Relative preservation of MTL on structural imaging (CT/MRI) is supporting a diagnosis of DLB, but is unusual in AD. Other supportive imaging biomarkers include generalized low uptake on perfusion SPECT or metabolic PET with reduced occipital activity, including the primary visual cortices (Minoshima et al., 2001; Sinha et al., 2012; McKeith et al., 2017). Parietotemporal reductions are observed in both AD and DLB, but occipital hypometabolism differentiated between the two conditions with 90% sensitivity and 71–80% specificity (Minoshima et al., 2001).

DLB is also characterized by relative preservation of posterior or mid-cingulate metabolism on FDG-PET, the so-called cingulate island sign. Occipital lobe hypometabolism and the cingulate sign, however, are not specific for DLB, as they can be observed in posterior cortical atrophy, a variant of AD (Bohnen et al., 2017).

On EEG, patients with DLB typically exhibit increased posterior slow wave activity relative to healthy controls and patients with AD (Cromarty et al., 2016). The presence of posterior (temporal) transient slow or sharp waves on EEG is included as a supportive feature of the condition in the diagnostic criteria (McKeith et al., 2017). The increased slow wave activity clinically correlates positively with the presence and severity of cognitive fluctuations (Bonanni et al., 2008). Similar to AD patients, DLB patients show greater coherence in the delta band, but reduced coherence in the alpha band (Malek et al., 2017; Andersson et al., 2008).

Other diagnoses

Neuroimaging is not yet used routinely for the assessment of late life depression (LLD), nor have large-scale classification studies been performed in this patient group. Many research studies have used neuroimaging to identify differences between patient and control groups. There are several reasons that have contributed to difficulties in translating their results into clinically useful diagnostic markers of LLD. First, there is frequently great heterogeneity in the anatomy of results reported. For example, while grey matter volume reductions in LLD have been most frequently reported within the frontal lobe and hippocampus, grey and white matter changes have also been observed in the parietal lobe, amygdala, putamen, and thalamus, particularly in late-onset illness (Sexton et al., 2012). Second, there is often a lack of specificity of results reported for LLD. For example, reduced hippocampal volume has also been reported in many other patient groups, including MCI, AD, FTD, and VD (van de Pol et al., 2006). Third, there is the question of what value a neuroimaging marker would have above and beyond the clinical assessment already used. An ideal marker would not only reliably discriminate between patient groups, but also predict outcome. For example, prediction of treatment response would allow the most likely effective treatment to be administered first, while prediction of first

episodes or relapses would provide an opportunity for preventative measures.

Predicting outcome

Neuroimaging techniques are not currently used in the clinic for predicting outcome, but significant research has been performed in this field. In particular, many studies have been performed that have the long-term aim of predicting conversion to AD from at-risk groups, including MCI and apolipoprotein E (ApoE) $\epsilon 4$ carriers.

MCI is a descriptive diagnosis that identifies patients referred with memory impairment beyond that expected for age and education, who do not display functional deficits, and so do not qualify for a diagnosis of dementia. A recent meta-analysis, however, calculated the annual conversion rate from MCI to AD to be only 5–10% (Mitchell and Shiri-Feshki, 2009).

Several T₁-weighted MRI studies have examined conversion from MCI to AD. Ferreira and colleagues (2011) performed a meta-analysis of six longitudinal VBM studies of MCI, in which 142 of 429 participants converted to AD. Conversion was associated with decreased grey matter in the left hippocampus and parahippocampal gyrus. Specificity and sensitivity rates in predicting conversion for individuals with MCI have also been calculated by some studies. For example, Devanand and colleagues (2008) used a model combining hippocampal and entorhinal volumes with functional and cognitive impairment measures, to predict conversion from MCI to AD with 85% sensitivity and 90% sensitivity. Markers of hippocampal atrophy do not, however, take into account the overall pattern of brain atrophy in AD. More recently, comprehensive quantitative metrics of typical brain atrophy in patients with AD that use composite measures across several brain regions or advance machine learning algorithms have been developed (Teipel et al., 2015). Generally, a major determinant of the prediction accuracy achieved in different MRI-based studies is the time to conversion in the patients analysed. The accuracy is higher in patients with MCI who are closer to developing AD.

Reduced white matter integrity has also been detected in people at higher risk of developing AD, including those with MCI and ApoE $\epsilon 4$ carriers. A meta-analysis of 21 case-control studies of MCI found that differences between MCI and controls paralleled the differences between AD and controls, but fewer regions reached statistical significance (Sexton et al., 2011). As with AD, several studies have reported a significant association between decreased MMSE and reduced FA in MCI (Ukmar et al., 2008; Bai et al., 2009; Mielke et al., 2009). The MMSE scores correlated with the FA in the splenium, the genu, and right frontal white matter (Ukmar et al., 2008). With regard to APOE $\epsilon 4$, a TBSS study identified a widespread pattern of elevated MD in APOE $\epsilon 4$ carriers aged 50–78 years compared with age-matched controls, and reduced FA in

carriers aged 20–35, again compared with age-matched controls (Heise et al., 2011).

Metabolic abnormalities in AD-related regions are found even in cognitively normal individuals at increased risk of AD (Mosconi et al., 2007). A meta-analysis of seven FDG-PET studies showed a sensitivity of 77% and specificity of 85% in predicting conversion from MCI to AD, compared with amyloid PET, for which sensitivity was 93% and specificity was 56% (Zhang et al., 2012). These results highlight that, clinically, the role of amyloid PET is more of an exclusionary one, as amyloid plaques are necessary, but not sufficient, for the development of AD.

Many studies have shown the predictive value of EEG measures for progression of healthy subjects to MCI and AD (Jeong, 2004). A seven-year follow-up study of 44 healthy participants with subjective memory complaints showed that EEG at baseline can predict conversion to MCI with 95% sensitivity and 94.1% specificity, and conversion to dementia with 96.3% sensitivity and 94.1% specificity (Prichep et al., 2006). These high values were achieved with ‘eyes-closed’ resting data. Subjects also had to discontinue any centrally acting medication at least two weeks before the baseline scan, which probably limits the potential clinical use. The authors further did a post-hoc logistic regression analysis based on nine quantitative (Q)EEG baseline variables, and variables with the highest significance in their prediction equation were mean frequency of the total spectrum, mean frequency in the delta band, absolute power across all frequency bands on the right hemisphere, and absolute power in the theta frequency band. Quantitative EEG may also have a role in predicting the progression from MCI to DLB. Bonanni and colleagues (2015) followed up 47 MCI subjects for three years. At the end of the follow up, 20 patients had developed probable DLB and 14 had probable AD, with the other patients remaining stable or developing other types of dementia. All DLB patients showed the typical of early DLB EEG abnormalities at admission, while 93% of the patients who developed probable AD maintained a normal EEG throughout the study (Bonanni et al., 2015).

Several studies have used EEG also to investigate the effect of *ApoE* genotype on brain function. In AD patients and in healthy subjects, differences between *ApoE* $\epsilon 4$ carriers and non-carriers were reported. This affected task-related ERP amplitudes and latencies (Espeseth et al., 2009), as well as resting-state EEG measurements (Babiloni et al., 2006).

Understanding illness mechanisms

Neuroimaging can contribute in different ways to the question how and why diseases develop. Functional and structural measures can be used to evaluate the effects of drug treatment, investigate the effects of lifestyle factors on the brain and disease risk, and provide insights into mechanisms that underlie genetic susceptibility to diseases.

With respect to AD, examples of these approaches are studies looking at the effect of cholinesterase inhibitor (ChEI) treatment on the brain (Venneri, 2007). In healthy subjects and AD patients, ChEI administration modulates brain function, and in AD patients it might slow down hippocampal atrophy. A double-blind randomized controlled trial of Donepezil in individuals with prodromal AD showed a 45% reduction in the rate of hippocampal atrophy in the treatment group compared with the placebo group after one year of treatment (Dubois et al., 2015). A follow-up study found that Donepezil-treated participants showed reduced rate of atrophy in the nucleus basalis of Meynert, the region with high concentration of cholinergic neurons projecting to the cortex (Cavedo et al., 2017). However, longitudinal studies of large patient populations are required to understand the long-term effects of ChEI administration. Given that, overall, only around 50% of patients show a positive response to medication, it is also important to investigate if structural or functional imaging measures can be used to predict the response to drug treatment.

Although there are genetic risk factors for AD development, there are important effects of lifestyle, e.g. diet, on AD risk. For example, several neuroimaging studies have shown effects of homocysteine levels on the brain, and among others plasma homocysteine levels depend on nutrition and vitamin supply. High plasma homocysteine levels increase the risk for AD (Seshadri et al., 2002), which might be due to increased cortical and hippocampal atrophy (den Heijer et al., 2003). Additionally, a recent study has reported that administration of B vitamin supplements can slow the rate of brain atrophy in MCI subjects (Smith et al., 2010). Therefore, neuroimaging markers can be used to identify lifestyle factors affecting AD, which may be important to delay disease onset and study preventative measures.

Illuminating the question as to how *APOE* genotype may affect susceptibility to AD, many studies have shown functional and structural differences between *APOE* $\epsilon 4$ carriers and non-carriers. For instance, activity within the default mode network differs between *APOE* $\epsilon 4$ carriers and non-carriers (Filippini et al., 2009). This resting-state network is of interest because amyloid plaque deposition seems to occur in regions that show high neuronal activity, such as the default mode network (Buckner et al., 2005). An association between neuronal activity and the processing of amyloid precursor protein has also been shown in vitro (Kamenetz et al., 2003), which suggests the hypothesis that genetically based differences in neuronal activity may play a role in AD development.

In LLD, neuroimaging studies have played a key role in the development and assessment of the vascular depression hypothesis. The vascular depression hypothesis proposes that cardiovascular factors may 'predispose, precipitate, or perpetuate' late-onset depression (LOD) (typical age of onset is +60 years) (Alexopoulos et al., 1997). Specifically, vascular factors are hypothesized to cause white matter damage within frontal-subcortical circuits (Alexopoulos et al., 1997; Alexopoulos, 2002).

In support of this hypothesis, LOD has often been found to be associated with more frequent and severe WMH compared with early-onset depression (EOD) (Herrmann et al., 2008). More frequent and severe, WMH have also been linked to poor antidepressant treatment response in LLD (Hickie et al., 1997; Hickie et al., 1995; Simpson et al., 1998). Expanding on this research, Sheline and colleagues (2010) have reported that WMH severity predicted Montgomery-Åsberg Depression Rating Scores (MADRS) over a 12-week course of treatment. Although some studies of WMH have employed automated methods, the majority of studies have used rating scales that can suffer from intra- and interrater reliability and a lack of anatomical specificity, and may also be insensitive to subtle changes in WM integrity. DTI studies of LLD overcome many of these limitations and have also provided support for the vascular hypothesis of depression. For example, Sexton and colleagues (2012) found that later age at onset was significantly associated with reduced FA of widespread tracts, in particular, the anterior thalamic radiation and superior longitudinal fasciculus. Similarly, Framingham Stroke scores predicted greater disruption of white matter connectivity (Allan et al., 2012).

Understanding resilience: Neuronal scaffolding

Ageing is characterized by decreasing grey matter density, reducing white matter integrity, and (somewhat paradoxically) increasing neuronal activity. For example, fMRI studies report increased bilateral activation of frontal and other association cortices in older as opposed to younger subjects, which is associated with better cognitive performance (Cabeza et al., 2002; Cabeza et al., 1997; Grady et al., 1999; Reuter-Lorenz et al., 1999; Rypma et al., 2001; Reuter-Lorenz, 2002; Fera et al., 2005). Hippocampal underactivity in well-functioning older subjects is combined with increased bilateral frontal activation when compared with younger volunteers (Morcom et al., 2003; Cabeza et al., 2004; Gutchess et al., 2005; Persson et al., 2006). This increase in activity has been interpreted as a compensatory process, i.e. the brain has to work harder to achieve the same level of performance. A number of authors have converged on the view that it may delay performance failure and clinical decompensation even in the face of progressive atrophy of critical brain structures (e.g. hippocampus) and it is accompanied by subjective awareness of cognitive problems or increased effort during task performance (Buckner, 2004; van Norden et al., 2008). The concept of neuronal scaffolding is a formulation of this general idea that successful ageing is associated with increased recruitment of additional neuronal resources in the face of deteriorating brain structure (Reuter-Lorenz and Cappell, 2008; Han et al., 2009; Park and Reuter-Lorenz, 2009). Scaffolding is a process that results in changes in brain function through strengthening of existing connections, formation of new connections, and disuse of connections that have become weak or faulty (Park and Reuter-Lorenz, 2009). Consistent with this, a posterior-anterior shift of brain activity can be observed with increasing age, suggesting that frontal lobe

networks are preferentially activated in a compensatory manner and so may provide the necessary secondary scaffold (Davis et al., 2008). Therefore, damage to the primary structure involved in a neurocognitive task (for example, the hippocampus in memory) must exceed a certain threshold to reveal the presence of objective memory impairment. However, a parallel process affecting the compensating networks (typically generalized vascular pathological change) may worsen the impact of the primary pathology or even be necessary to reveal a classical clinical condition (Buckner, 2004). This dual mechanism may explain the biphasic clinical course of initial compensated memory impairment with insight, followed by dementia and loss of function in AD (Buckner, 2004). While hippocampal lesions occur early and are the locus of maximum plaque and tangle formation, older people in general and AD patients in particular show a deterioration in the frontal executive network that is characterized by reduction in fluid intelligence, i.e. abstract thinking and reasoning. Structurally, there may be WMH, reductions in white matter integrity, and frontal atrophy. This putative mechanism may be generally applicable because both whole-brain and hippocampal atrophy trajectories have been related to the onset of cognitive impairment and dementia: in one study hippocampal atrophy preceded dementia by three years and whole-brain atrophy by one year (Ridha et al., 2006). Consistent with this, hippocampal atrophy rates have been shown to predict MCI, while global atrophy rates predicted dementia onset (Henneman et al., 2009). In summary, successful ageing is characterized by more anterior, less lateralized, and more coordinated brain activity. The scaffolding theory of ageing has been proposed to explain the processes behind the differing patterns of activation found in ageing. Individual differences in the brain's ability to scaffold may explain the heterogeneity in ageing.

Conclusion

It has taken half a century to develop methods that allow us to examine brain structure and function in vivo. These secrets have been well guarded by the compact packaging and the complex structure of our brains. While giant strides are being made in unravelling aspects of normal and abnormal brain function, analysing this most complex of all systems will take some time to achieve. Obvious limits are given by ethics and by the absence of credible (animal or computing) models for most human psychiatric disorders. It will take all our ingenuity to develop insights and methods that will be of benefit to our patients. We may, nevertheless, be the last generation of clinicians who can claim with quiet satisfaction that our attentive interview and expert examination are as good as any brain imaging currently available to make a diagnosis and decide on the best management for our patients.

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Psychopharmacology

Chapter: Psychopharmacology

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Introduction

This chapter examines the factors to consider when prescribing psychotropic drugs in older people. It reviews the major physiological changes that occur in old age and the effects that these changes have on the pharmacokinetics and pharmacodynamics of drugs, in particular psychotropic medication. It discusses the problems associated with polypharmacy and explains the potential mechanisms involved in the occurrence of adverse drug reactions and drug-drug interactions. It also investigates the reasons for non-adherence to medication in elderly patients and highlights the importance of establishing adherence before prescribing medication, especially in this population. In addition, it reviews the evidence for the risks associated with the use of antipsychotic drugs and anticholinergic drugs in older people and provides guidance on prescribing these drugs where necessary.

Complexities associated with medication use in older people

The use of pharmacological agents in older adults is one of the most complex aspects of patient care. Clinicians must display expert knowledge on and careful consideration of the various factors involved. Older people exhibit an unexpected or exaggerated response to drug therapy when compared to their younger counterparts of the same body weight and gender, which can often be explained through pharmacokinetic or pharmacodynamic changes. Understanding the common physiological changes seen in ageing is helpful to anticipate the changes expected in pharmacokinetic parameters. The pharmacodynamic variations seen in older patients may also increase or decrease sensitivity to a drug independently of the pharmacokinetic changes (Hutchison and O'Brien, 2007). In addition, age is known to be associated with increased prevalence of multiple chronic illnesses frequently requiring the use of complex therapeutic regimens. Age-related physiological changes as well as the presence of comorbidity and polypharmacy will complicate drug therapy in older people.

Older adults are conventionally defined by a chronological age of 65 years and older because there are as yet no biological markers to define old age. Several processes are involved in ageing including progressive impairments in the functional reserve of multiple systems and organs and reduced ability to respond to environmental demands. The reduced efficacy of homeostatic mechanisms is a fundamental feature of ageing but the decline in functional reserve varies markedly between elderly individuals (Turnheim, 2003). Very old individuals tend to become frail, a syndrome defined as an excessive reduction of lean body mass, loss of skeletal muscle (sarcopenia), chronic under-nourishment, reduced function, and poor endurance as well as neuroendocrine and immune dysfunctions (Walston and Fried, 1999). The prevalence of diseases increases with advanced age, leading to extensive use of medications. Almost half of people over 65 years of age take at least five regular medicines a day (Gao et al., 2017). Consequently, adverse drug reactions are more frequent and more serious in older people (Doucet and Queneau, 2005; Lavan and Gallagher, 2016) and drug interactions occur more often (Herrlinger and Klotz, 2001).

Age-related changes in pharmacokinetics

Pharmacokinetics is the branch of pharmacology concerned with the movement of drugs within the body. Ageing is generally characterized by changes in all phases of pharmacokinetic processes: absorption, distribution, metabolism, and excretion (see Table 13.1).

Table 13.1 Pharmacokinetic changes due to ageing and effect on dosing of psychotropic drugs.

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Age-related physiological changes	Pharmacokinetic parameter	Effect on pharmacokinetic parameters	Impact on psychotropic drug dosing
Reduced gastric acid secretion	Absorption	Slightly decreased absorption	Minimal for most drugs
Decreased gastrointestinal motility			
Slowed intestinal transit time			
Delayed gastric emptying			
Reduced splanchnic blood flow			
Reduced bowel surface area			
Increased body fat	Distribution	Increased volume of distribution and half-life for lipophilic drugs	Moderate for some drugs, e.g. phenytoin, diazepam
Decreased lean body mass			
Decreased total body water		Increased plasma concentration of water-soluble drugs	
Decreased serum albumin concentrations		Increased free-fraction of highly protein-bound acidic drugs	
α_1 -glycoprotein concentrations tend to increase		Decreased free-fraction of basic drugs	

Psychopharmacology

Reduced liver mass Reduced liver blood flow Reduced hepatic metabolic function	Metabolism	Less effective first pass metabolism and phase I metabolism	Moderate for some drugs e.g. nortriptyline
Reduced renal mass Reduced renal blood flow Reduced glomerular filtration rate (GFR) Reduced filtration fraction Reduced tubular secretion	Excretion	Impaired renal elimination of water-soluble drugs	Major for drugs that are extensively eliminated by the kidneys, e.g. lithium, gabapentin

Minimal = no impact on dosing anticipated

Moderate = some drugs may require dosage adjustments and monitoring

Major = accurate dose adjustments and monitoring required
Source: data from Corsonello A., Pedone C., and Incalzi A. (2010). Age-related Pharmacokinetic and Pharmacodynamic Changes and Related Risk of Adverse Drug Reactions. *Current Medicinal Chemistry*, 17, 571-584; data from Hutchison L. and O'Brien C. (2007). Changes in Pharmacokinetics and Pharmacodynamics in the Elderly Patient: *Journal of Pharmacy Practice*, 20(1), 4-12.

Absorption

In the ageing gastrointestinal (GI) tract, several physiological changes have been observed, including reduced gastric acid secretion resulting in increased gastric pH, decreased gastrointestinal motility, slowed intestinal transit time, and delayed gastric emptying, as well as reduced splanchnic blood flow and bowel surface area (Klotz, 2009; Hutchison and O'Brien, 2007; Corsonello et al., 2010). Oral medicines have been extensively studied to determine whether these changes have an effect on their absorption. However, since most drugs undergo passive diffusion in the GI tract, they may experience a delay in absorption; there is no

overall change in the extent of their absorption. Thus, there may be a delay in the time to reach maximum concentration after the first dose of medication and the area under the curve (AUC) graph appears flattened, but not diminished. The area under the plasma drug concentration-time curve reflects the actual exposure of drug in the body after administration of a dose. It is dependent both on the rate of elimination of the drug from the body and the dose administered.

In summary, with long-term medication that reaches steady state, no clinically significant changes in absorption occur. However, important changes do occur for certain agents that require a low pH or that undergo active absorption processes (e.g. glucose, calcium, vitamin B₁₂). For these agents, a reduction in absorption may be seen. In contrast, due to reduced gastric acid secretions seen in older people, enteric coated tablets tend to undergo an increased rate of absorption since the coating breaks down more rapidly in alkaline fluid (McLean and Le Couteur, 2004; Hutchison and O'Brien, 2007).

Absorption of drugs from other routes of administration can also be altered in older people. Although with age there is atrophy of the epidermis and dermis, which can result in a reduction in the skin's barrier function, the rate of transdermal drug absorption may in fact be diminished because of reduced tissue blood perfusion. This is also true for the subcutaneous route of administration. Intramuscular injections can lead to erratic absorption of drugs in older people (Turnheim, 2003).

Distribution

The distribution of drugs around the body can be significantly affected by changes in body composition occurring in advanced age. In general, body fat mass increases by 20–40%, while total body water and lean body mass decrease by 10–15% (Corsonello et al., 2010; Turnheim, 2003). As a result, the volume of distribution of lipophilic drugs (e.g. diazepam and chlordiazepoxide) may increase leading to prolonged half-life and time necessary to reach steady state concentration during repeated drug administration (Hutchison and O'Brien, 2007). For water-soluble drugs, however, the volume of distribution decreases resulting in higher plasma concentrations and lower starting dose requirements (e.g. lithium) (Corsonello et al., 2010; Turnheim, 2003).

In general, the changes seen in plasma protein binding appear to be less important for drug therapy in older people. Drugs circulating in blood may be bound to plasma proteins, with only the unbound fraction being pharmacologically active. Serum albumin concentrations can be slightly decreased or remain unchanged in healthy older people, but are significantly lower in frail or malnourished patients. The decrease in albumin can result in an increase in the free fraction of drugs highly bound to albumin, causing unexpected drug toxicity when they are first administered to a patient, until their steady state equilibrium is established. Phenytoin and warfarin are examples of drugs with high free

serum concentrations, despite having the same total concentration (Hutchison and O'Brien, 2007). Psychotropic drugs with a high percentage of protein binding include diazepam, lorazepam, valproate (Hutchison and O'Brien, 2007), and haloperidol (Koyama et al., 2003). The concentrations of α_1 -glycoprotein, which binds primarily to alkaline drugs, tend to increase with age (Corsonello et al., 2010). Since fewer drugs with a narrow therapeutic index bind to this protein, adverse effects are not generally attributed to this change.

Metabolism

The effect of age on hepatic drug metabolism continues to be a controversial issue. Although the metabolism of drugs occurs primarily in the liver, enzymes in the kidney and GI tract may also be involved. A decrease in mass of the liver and kidney accompanied by a decrease in their function plays an important role in the reduction in drug metabolism in older people. Hepatic volume is known to decrease with ageing by about 20–30% and hepatic blood flow is reduced by about 20–50% (Hutchison and O'Brien, 2007; Klotz, 2009; Corsonello et al., 2010). Despite these changes, routine clinical tests of liver function do not change significantly with advancing age, although the serum albumin concentration may decrease slightly (Turnheim, 2003).

The metabolism of drugs in the liver is influenced by the following: hepatic perfusion, intrinsic clearance (capacity/ activity of metabolising enzymes), uptake clearance, and protein binding (Corsonello et al., 2010). Whether the metabolic clearance of a drug is decreased or unchanged in old age has been attributed to the property of the drug in terms of whether it undergoes high or low intrinsic clearance. Some drugs with high intrinsic clearance are rapidly metabolized in the hepatocytes and the rate of drug loss is limited by hepatic blood flow. Since blood flow to the liver declines with age, drugs exhibiting high extraction therefore display an age-related decrease in metabolic clearance. The term 'flow-limited' metabolism is used in these cases and examples of such drugs include amitriptyline and imipramine. Other drugs with low intrinsic clearance are slowly metabolized by hepatic enzymes and the rate of elimination is mainly dependent on enzyme activity. The metabolic clearance of these drugs is, in most cases, *not* reduced in old age as it is not dependent on hepatic blood flow, but rather on the total tissue content of metabolising enzymes ('intrinsic clearance'). This type of metabolic clearance is called 'capacity limited' and examples of drugs include diazepam and valproate (Turnheim, 2003; Corsonello et al., 2010).

Therefore, age-related changes in the liver have the potential to impact on the presystemic metabolism (first-pass effect) and thus the bioavailability of drugs with high hepatic clearance after oral administration. Although the effect on bioavailability is unpredictable, the age-related changes in the liver have the potential to result in a

significant and variable increase in bioavailability for some drugs after oral administration (McLachlan and Pont, 2012).

Changes in hepatic blood flow and intrinsic clearance, however, do not explain the age-dependent reduction in hepatic metabolism of all drugs. For example, theophylline still experiences reduced metabolism in old age although it undergoes capacity-limited metabolism (Turnheim, 2003).

Before their final excretion, the majority of drugs have to undergo biotransformation to more polar (water-soluble) metabolites by several cytochrome P450 (CYP) enzymes. In general, inter-individual variation in metabolic drug clearance by CYP enzymes exceeds the decline caused by ageing. Phase I metabolism primarily consists of oxidation (through the CYP enzyme system in the liver), reduction, and hydrolysis. Research into whether phase I metabolism is significantly reduced in older people has yielded inconsistent results. The CYP 2C19 shows a reduction with ageing but CYP 2D6 does not. The other isoenzymes (1A2, 2C9, 2E1, and 3A4) show marked variability but only a minor decrease or no change at all. Studies comparing young adults with fit elderly individuals and frail elderly individuals found little difference between the young adults and fit elderly people, but a significant reduction in esterase activity (another phase I pathway) was seen in the frail elderly people. In view of this wide variability, it is safer in older people to reduce the dosages of drugs that undergo phase I metabolism, e.g. chlordiazepoxide, diazepam, zolpidem, amitriptyline, selective serotonin reuptake inhibitors (SSRIs), venlafaxine, and risperidone (Hutchison and O'Brien, 2007).

Phase II metabolism involves conjugation (the attachment of an ionized group to the drug) and includes glucuronidation, acetylation, or sulfation. Conjugation reactions are usually unchanged in old age as the activities of glutathione transferase and UDP glucuronosyltransferase are not altered (Le Couteur and McLean, 1998). Therefore, no dose adjustments are usually required on the basis of age alone. Examples of psychotropic drugs that undergo phase II metabolism include lorazepam, oxazepam, zaleplon, and valproate (Hutchison and O'Brien, 2007). Studies have highlighted, however, that glucuronidation is affected by frailty, with frail older people having significantly reduced metabolic capacity in the formation of conjugated metabolites (McLachlan and Pont, 2012; Hilmer et al., 2005).

Excretion

The ageing process gives rise to important modifications in kidney structure and function. Older people tend to have a reduction in renal mass, renal blood flow, glomerular filtration rate (GFR), filtration fraction, and tubular secretion. At a microscopic level, the ageing kidney is characterized by increased fibrosis, tubular atrophy, and arteriosclerosis. A decrease of about 10% per decade in glomerular filtration rate can generally be expected. A measured creatinine clearance is used as a surrogate for GFR, but can be inaccurate because of the many problems

associated with a 24-hour urine collection, as well as the costs involved. The use of serum creatinine level on its own may lead to misleading estimates of renal function because the daily production of creatinine may be significantly reduced in older people as a result of decreased muscle mass, reduced exercise, and dietary meat intake. Thus, the serum creatinine may remain within the normal range despite a reduction in creatinine clearance (Hutchison and O'Brien, 2007; Corsonello et al., 2010). For these reasons, equations for estimated GFR (eGFR) were developed (Garasto et al., 2014).

The Cockcroft and Gault equation estimates the creatinine clearance which in turn estimates GFR in ml/min. The formula was originally published as (Cockcroft and Gault, 1976):

$$\text{CrCl (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times (0.85 \text{ in women})}{72 \times \text{Serum creatinine (mg/dL)}}$$

When serum creatinine is measured in $\mu\text{mol/L}$:

$$\text{CrCl (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times \text{Constant}}{\text{Serum creatinine } (\mu\text{mol/L})}$$

where *Constant* is 1.23 for men and 1.04 for women. Ideal body weight should be used for patients with extremes of body weight.

One interesting feature of the Cockcroft and Gault equation is that it shows how dependent the estimation of creatinine clearance is based on age.

Various other equations for estimating GFR have been developed, for instance, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, which is the now-preferred one for assessing renal function in kidney disease (NICE CG182). However, when calculating drug doses, the estimated creatinine clearance from the Cockcroft and Gault equation should be used.

Age-related changes in pharmacodynamics

Pharmacodynamics is the branch of pharmacology concerned with the biochemical and physiological effects of drugs at their site of action. It relates to the concentrations of drug at the receptor site, the interaction between the drug and its receptor, and the homeostatic regulation. Several patient specific factors, e.g. age, gender, ethnicity, genetics, and disease, are all known to influence pharmacodynamics (Bowie and Slattum, 2007; Corsonello et al., 2010).

In general, apart from its concentration at the site of action, the magnitude of a drug's effects also depends on the number of receptors at the target organ, the ability of the cells to respond to receptor occupation (signal transduction), and the counter-regulatory processes that tend to preserve the original functional equilibrium. An increase in drug

sensitivity is assumed when the response to a given serum concentration is enhanced. Age-related changes in pharmacodynamics can occur at any level: the receptor level, signal transduction level, or from the changes in homeostatic mechanisms (Turnheim, 2003).

While pharmacokinetic modifications associated with age are, to some extent, predictable (due to known changes in body composition and function), the convoluted and multiform interaction between altered kinetic and reduced homeostatic response make pharmacodynamic changes with age a very complex process. As a result, there are no set rules to help guide clinicians in this area, and the age-related changes in the pharmacodynamics of a drug must be considered separately for each individual drug (Corsonello et al., 2010).

The central nervous system (CNS) is a particularly vulnerable drug target in older people, since ageing causes neuronal loss in several brain regions and a reduction in brain weight (Turnheim, 2003). As a result, older people are very sensitive to the adverse effects of psychotropic drugs, especially delirium, arrhythmias, and postural hypotension. The number of dopaminergic neurons and dopamine D₂ receptors decreases in older people, leading to extrapyramidal symptoms with antipsychotic drugs when a certain threshold of neuronal loss is reached. The number of cholinergic receptors and neurons is also decreased, which is thought to affect cognitive function. In addition, although the exact mechanism for this is unknown, benzodiazepines induce sedation, ataxia, and confusion at lower doses and plasma concentrations in older adults than in younger people. This is possibly due to age-dependant changes identified in the GABA_A-benzodiazepine receptor complex. Benzodiazepines can also cause short-term memory impairment and contribute to cognitive disturbances in this population (Mangoni and Jackson, 2003; Turnheim, 2003).

Since homeostatic mechanisms are reduced in old age, when a pharmacological disruption of a physiological function occurs, more time is required to regain the original steady state because the counter-regulatory measures are diminished. Thus, despite the reduction in receptor numbers and responsiveness, drug effects are attenuated less in older people, the reactions may be stronger, and the incidence of adverse effects is higher when compared to young people. Examples include drug-induced postural hypotension that can lead to syncope and falls (Turnheim, 2003).

The potential for adverse effects in older people is also increased with anti-epileptic drugs where cognitive impairment and haematological toxicity are observed. In addition, although usually irrelevant in the young, cardiac effects of phenytoin or carbamazepine may be life threatening in older patients. Similarly, tricyclic antidepressants and antipsychotic drugs such as haloperidol may have adverse cardiac effects, e.g. prolongation of QT interval, and cause life-threatening ventricular tachyarrhythmia (torsade de pointe) (Turnheim, 2003).

The blood-brain barrier (BBB)

The structure of the blood brain barrier (BBB) comprises endothelial cells with tight junctions in a collagen matrix allowing only small, lipid-soluble, unpolarized molecules to pass from capillary blood to brain tissue. Thus, molecular size, lipophilicity, and polarity are all factors influencing the extent to which substances can penetrate the CNS under normal conditions. Several conditions, however, can increase the permeability of the BBB, including increasing age, comorbid disorders such as diabetes, Parkinson's disease, and Alzheimer's disease, certain medicines, trauma, and stress (Abbott et al., 2010; Esposito et al., 2001). As a result, the blood brain barrier can become 'leaky', allowing compounds through that would not normally be able to penetrate the CNS. A mechanism known to reduce CNS exposure involves permeability-glycoprotein (P-gp), an active CNS efflux transporter that can actively pump agents moving across the BBB from the cerebral vasculature back into the systemic circulation. Drugs that are recognized by P-gp are referred to as P-gp substrates (van Assema et al., 2012). Nevertheless, age-associated decline in P-gp function also occurs, facilitating the accumulation of toxic substances in the brain and thus increasing the risk of neurodegenerative pathology and exposing the brain of older individuals to excessive levels of drugs (Corsonello et al., 2010). More research into age-related changes in the BBB is required to determine whether the alterations in BBB integrity in older people contributes to the enhanced sensitivity to many psychotropic drugs (including benzodiazepines) experienced in this population (Zeevi et al., 2010).

Adverse drug reactions (ADR)

The prevalence of adverse drug reactions (ADRs) increases with age, with twice as many patients aged 65 years and older being admitted to hospital because of ADR-related problems compared with their younger counterparts. More than 50% of these admissions are preventable (Lavan and Gallagher, 2016). It has been suggested that rather than being an independent risk factor, age may simply be a marker for comorbidities, altered pharmacokinetics, and polypharmacy, all of which increase the risk of ADRs (Hilmer et al., 2005).

ADRs are difficult to recognize in older people as they often present with non-specific symptoms such as falls, cognitive impairment, or constipation, all of which have several aetiologies. The risk of falls is increased by certain chronic conditions such as osteoarthritis, visual impairment, and myopathy, but several medications, including antipsychotics and benzodiazepines, can also independently increase the risk of falls. This can make it very difficult to identify the precise cause of a fall. Nevertheless, potential ADRs should be part of every differential diagnosis in older patients. Failure to recognize an ADR can result in a prescribing cascade whereby a new drug is prescribed to treat the adverse effect of the culprit drug, thus exposing the individual to continued and increased risk of ADRs (Lavan and Gallagher, 2016).

Examples of such practice include the prescribing of an anticholinergic drug to treat extrapyramidal symptoms caused by antipsychotic drugs, or urinary frequency caused by acetylcholinesterase inhibitors.

Anticholinergic drugs in turn can cause cognitive impairment, delirium, blurred vision, constipation, and so on (see Fig. 13.1).

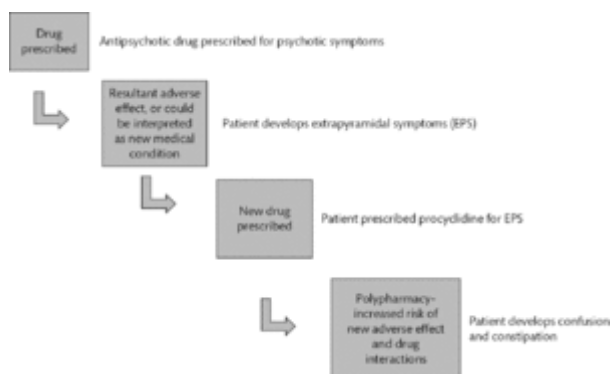


Fig. 13.1

Example of prescribing cascade in older people.

Reproduced with permission from Merel, S.E., and Douglas, S.P. Common Drug Side Effects and Drug-Drug Interactions in Elderly Adults in Primary Care. *Journal of the American Geriatrics Society*, 65(7): 1578–1585. Copyright © 2017, Copyright the Authors Journal compilation, The American Geriatrics Society. <https://doi.org/10.1111/jgs.14870>.

Polypharmacy

Polypharmacy, commonly defined as the use of multiple drugs, or more than are clinically indicated, is strongly predictive of ADRs (Lavan and Gallagher, 2016). Polypharmacy increases the risk of adverse events as a result of both the cumulative effect of ADRs to each drug and drug-drug interactions. Many predictable drug-drug interactions occur through the induction or inhibition of cytochrome p450 pathways of hepatic metabolism (Hilmer et al., 2005). Polypharmacy is common in older people due to the number of comorbidities that occur with increased age. Clinicians are often not aware of all the drugs their elderly patients are taking. Patients might receive prescriptions from several different clinicians and could potentially take them to be filled at different pharmacies. In addition, older people are more likely to be buying over-the-counter products for minor ailments. Mallet and colleagues showed that the risk of receiving inappropriate drug combinations is directly related to the number of clinicians prescribing drugs for an elderly patient (Mallet et al., 2007).

Drug-drug interactions

A drug-drug interaction can be defined as the effect that one drug has on another drug. Drug-drug interactions can be either pharmacokinetic or pharmacodynamic in nature. Pharmacokinetic drug interactions involve the effects of one drug on the absorption, distribution, metabolism, or excretion of another drug. These interactions can result in changes in serum drug concentrations and might therefore change the clinical response. The most frequent pharmacokinetic drug interactions involve several isoenzymes of the hepatic cytochrome P450 (CYP) and drug transporters such as the P-glycoprotein and organic anion transporters. Drugs that are substrates, inhibitors, or inducers of CYP450 isoenzymes (e.g. CYP3A4, CYP2D6) are frequently involved in drug-drug interactions (Mallet et al., 2007) (see Table 13.2).

Table 13.2 Psychotropic drugs and their impact on the cytochrome P450 system.

Psychopharmacology

Substrates		Inhibitors		inducers
CYP1A2				
agomelatine amitriptyline* asenapine bupropion* chlorpromazine clomipramine* clozapine duloxetine fluphenazine	fluvoxamine imipramine* melatonin mirtazapine* olanzapine perphenazine ?pimozide* zolpidem*	fluvoxamine moclobemide perphenazine		'barbiturates' carbamazepine modafinil* phenobarbital phenytoin
CYP2A6				
bupropion*		tranylcypromine		phenobarbital
CPY2B6				
bupropion methadone* nicotine sertraline*		fluoxetine* fluvoxamine memantine paroxetine* sertraline*		carbamazepine* modafinil* phenobarbital phenytoin
CYP2B7				

Psychopharmacology

buprenorphine*			Not known		Not known
CPY2C8					
zopiclone*			Not known		Not known
CPY2C9					
agomelatine* amitriptyline bupropion* fluoxetine* lamotrigine	phenobarbital phenytoin sertraline* valproic acid		fluoxetine* fluvoxamine modafinil valproate		carbamazepine St. John’s Wort
CPY2C19					
agomelatine* amitriptyline carbamazepine* citalopram clomipramine* diazepam escitalopram fluoxetine*	imipramine* ?melatonin ?methadone moclobemide phenytoin sertraline* trimipramine*		escitalopram* fluvoxamine moclobemide modafinil topiramate		carbamazepine St John’s Wort
CPY2D6					
amitriptyline	fluoxetine fluvoxamine	paroxetine perphenazine	amitriptyline asenapine	fluvoxamine* haloperidol	Not known

Psychopharmacology

‘amphetamines’ atomoxetine aripiprazole brexpiprazole cariprazine chlorpromazine citalopram clomipramine clozapine* donepezil* duloxetine escitalopram	fluphenazine galantamine haloperidol lloperidone imipramine methadone* mianserin mirtazapine* moclobemide nortriptyline olanzapine	pimozide* quetiapine* risperidone sertraline trazodone* trimipramine venlafaxine vortioxetine zuclopenthixol	bupropion chlorpromazine citalopram* clomipramine clozapine duloxetine escitalopram fluoxetine fluphenazine	levomepromazine methadone* moclobemide paroxetine perphenazine reboxetine* risperidone sertraline venlafaxine*	
CYP2E1					
Bupropion Ethanol			disulfiram paracetamol	Ethanol	
CYP3A4					
alfentanil alprazolam amitriptyline aripiprazole brexpiprazole buprenorphine bupropion* buspirone carbamazepine	diazepam donepezil dosulepin escitalopram* fentanyl fluoxetine* ?flurazepam galantamine haloperidol imipramine	nitrazepam perphenazine pimozide quetiapine reboxetine risperidone* sertindole sertraline* trazodone trimipramine*	fluoxetine fluvoxamine paroxetine perphenazine reboxetine*	asenapine? carbamazepine modafinil phenobarbital ‘and probably other barbiturates’ phenytoin St. John’s wort topiramate	

Psychopharmacology

cariprazine chlorpromazine citalopram clomipramine* clonazepam clozapine*	lurasidone methadone midazolam mirtazapine modafinil	venlafaxine zaleplon ziprasidone zolpidem zopiclone		

Drugs highlighted in **bold** indicate:

- predominant metabolic enzyme pathway or;
- predominant enzyme activity (inhibition or induction).

Drugs annotated with * indicate:

- known to be a minor metabolic enzyme pathway or activity (i.e. not demonstrated to be clinically significant).

Drugs in normal font (not bold and without *) indicate:

- metabolic enzyme pathway(s) or activity where significance is unclear or unknown

NB: Information on CYP function derived from individual SPCs and US Labelling (accessed November 2017).

The table does not include details of the effects of non-psychotropic drugs on CYP function. Reproduced with permission from The Maudsley Prescribing Guidelines in Psychiatry 2018. Taylor, Barnes & Young, 13th edition.

As well as the effect of co-administered drugs on CYP function, genetic polymorphisms associated with some enzyme pathways (e.g. 2D6, 2C9, 2C19 enzymes) may also account for the inter-individual variations in the metabolism of certain drugs. The effects of polymorphism and pharmacokinetic interaction are difficult to predict because some drugs are metabolized by more than one enzyme and so an alternative pathway may compensate when one enzyme pathway is inhibited (Taylor et al., 2018).

The P-glycoprotein (P-gp) is a drug transporter protein found in the gut wall and in the BBB. P-gp can eject (active process) drugs that diffuse (passive process) across the gut wall. Drugs that inhibit P-gp are therefore expected to increase the uptake of other drugs (that are substrates for P-gp) and drugs that induce P-gp are expected to reduce the uptake of drugs (that are substrates for P-gp). Many drugs that are substrates for CYP3A4 have also been found to be substrates for P-gp (Taylor et al., 2018).

Pharmacodynamic drug interactions relate to the pharmacological activity of interacting drugs. The outcome is an enhancement or reduction in the therapeutic effects or side-effects of a specific drug by another (Mallet et al., 2007). An example of a pharmacodynamic drug interaction causing an enhancement in effects includes the addition of a benzodiazepine to an antipsychotic drug regime, producing excessive sedation. Conversely, an example of a pharmacodynamic drug interaction causing a reduction in therapeutic effect includes the addition of an anticholinergic drug such as oxybutynin used for urinary frequency to an acetylcholinesterase inhibitor for example donepezil. The anticholinergic drug will negate the effects of donepezil.

Stopping medications can also be associated with adverse drug effects related to withdrawal of the drug, recurrence of the underlying condition, or alterations in pharmacokinetics and pharmacodynamics of the patient's other medications (Hilmer et al., 2005).

Medication adherence in older people

Medication adherence is crucial when treating chronic conditions. Therefore, it is even more so when treating older people. Adherence to medication has always been a major issue in healthcare but more so in the elderly population. Reasons for poor adherence are multifactorial and can be classified into patient factors, medication factors, health care provider or system factors, and socioeconomic factors. Examples of patient factors affecting adherence include poor memory or cognitive deficits, depression, poor dexterity, and visual or hearing impairment. Medication factors include aspects of packaging and formulation, e.g. patients may be unable to open a container or swallow large tablets, or may have to manage complicated drug regimens. Healthcare provider or system factors include poor communication, lack of patient involvement,

lack of patient education or follow up, and socioeconomic factors involve the lack of caregivers or caregiver's burden (Yap et al., 2016).

Establishing preceding adherence upon admission to hospital is crucial in order to prevent the occurrence of ADRs. If poor adherence is not identified and medication is given as prescribed (or dose is increased due to the false assumption of lack of efficacy), patients will be at risk of ADRs, particularly older patients. An important example of this in psychiatry is lamotrigine, where dose titration should be repeated after an interval of more than five days—otherwise serious skin reactions can occur.

Antipsychotic use in older people with dementia

For many years, it has been common practice to use antipsychotic drugs in older people with dementia to manage behavioural and psychological symptoms. However, in the last decade, antipsychotics have been associated with an increased risk of stroke and mortality in this population. The increased risk exists with all antipsychotic drugs, both typical and atypical. While the exact mechanisms for this are still unknown, several theories exist. It is thought that orthostatic hypotension may potentially aggravate the deficit in cerebral perfusion in an individual with cerebrovascular insufficiency or atherosclerosis, thus causing a stroke. Tachycardia may also decrease cerebral perfusion or dislodge a thrombus in a patient with atrial fibrillation. There could be a rebound excess of catecholamines with vasoconstriction after an episode of orthostatic hypotension, thus aggravating cerebral insufficiency. In addition, hyperprolactinaemia could (in theory) accelerate atherosclerosis, in turn increasing the risk of a stroke. Sedation, often experienced in medicated older people, might cause dehydration and then haemoconcentration. Each of these factors are all possible mechanisms for the increased risk of cerebrovascular events in older people (Smith and Beier, 2004).

In view of this, antipsychotic drugs should not be used routinely to treat agitation and aggression in people with dementia (Corbett et al., 2014). Risperidone is the only drug licensed in the UK for the management of non-cognitive symptoms associated with dementia and is therefore the agent of choice. It is specifically indicated for short-term treatment (up to six weeks) of persistent aggression in patients with moderate to severe Alzheimer's disease who are unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others. Risperidone is licensed up to 1mg twice a day, although optimal dose in dementia has been found to be 500mcg twice a day (1mg daily) (BNF, Jan 2018).

Alternative antipsychotic drugs may be used (off-licence) if risperidone is contraindicated or not tolerated, but antipsychotics, in general, should only be prescribed in dementia after careful risk assessment, balancing the cerebrovascular risk (taking into account hypertension, diabetes, smoking, atrial fibrillation, and previous stroke), discussion of possible

risks and benefits with carer (and patient if she/he has capacity), and clear documentation of the above (Corbett et al., 2014).

Anticholinergic drugs and cognitive impairment

Older people with dementia are more susceptible to cognitive side effects of drugs. Drugs may affect cognition through their action on cholinergic, histaminergic, or opioid neurotransmitter pathways or through more complex actions. While anticholinergic drugs have been known to cause adverse effects, e.g. confusion, disorientation, hallucinations, and delirium, in older people, more recently, long-term use of these agents has also been associated with an increased risk of cognitive decline, dementia, and death (Carriere et al., 2009; Fox et al., 2011). In addition, anticholinergic drugs have been shown to directly oppose the action of acetylcholinesterase inhibitors used in dementia, thus reducing or negating any therapeutic effects. Nevertheless, studies have frequently shown that up to half of patients with dementia who are prescribed cholinesterase inhibitors are also taking drugs with anticholinergic activity (Carnahan et al., 2004).

Some drugs such as amitriptyline, clozapine, or promethazine are widely known to have anticholinergic properties, whereas other drugs are less likely to be associated with these effects (e.g. olanzapine, quetiapine, and citalopram). Cognitive impairment, particularly memory dysfunction, results from antagonism of M_1 and to a lesser extent M_2 or M_4 muscarinic receptors, which are particularly abundant in the CNS and are thought to mediate cholinergic effects on cognition. For an anticholinergic drug to significantly affect cognition, it not only needs to act on these specific muscarinic receptors, but also needs to be able to penetrate the BBB. In order to identify those drugs that have anticholinergic effects on cognition and those that are safe in patients with dementia, the anticholinergic effect on cognition (AEC) scale was developed and can be accessed on the web-based application Medicheck (<http://www.medicheck.com/>) (Bishara et al., 2017).

Research in older adults

Information on drug safety in older people is sparse, making it difficult to predict their response to medications. Unfortunately, there is very little clinical trial evidence to guide prescribing in this population since elderly patients with comorbid conditions are frequently excluded from clinical trials (Van Spall et al., 2007). As a result, the evidence coming from these studies may not be applicable to older people. Similarly, clinical practice guidelines may also be biased as they are frequently based on the evidence coming from these clinical trials and older people are a very heterogeneous group. In addition, randomized trials are usually not powered to detect safety-related outcomes and therefore only data from observational studies are usually available (Corsonello et al., 2010).

Conclusion

Older people are particularly susceptible to adverse effects of drugs because of the age-associated changes that occur in pharmacokinetic and pharmacodynamic properties, the large number of drugs used in this population, and the increased risk of comorbid diseases.

When considering the effect of ageing on drug disposition and metabolism in older people, confounding factors such as frailty, comorbidities resulting in the possibility of drug-disease interactions and in the case of polypharmacy drug-drug interactions, impairments in organ function and homeostasis, as well as problems with adherence due to reduced dexterity and memory problems all have to be considered. It is important to recognize the heterogeneity of drug response in this group.

While there are no simple rules for prescribing that can be applied to the entire elderly population, it is important to consider some kind of dosage reductions may be required, as well as careful dosing, slow titration, and monitoring of drug action. The general slogan 'start low and go slow' is often used. Only one new medication should be commenced at any one time so that clinicians are able to recognize potential ADRs more easily. Patients and carers should receive clear and concise information about new medicines, including any potential side effects (Merel and Douglas, 2017) and the time frame in which they are most likely to occur. Clinicians should refrain from treating every symptom with a new drug, particularly since the symptoms in question may be due to an adverse effect of a current medication.

Since very little clinical trial evidence exists for older people, it is very difficult to guide prescribing in this area. Clinical decisions must therefore be made for each individual with vigilant monitoring for efficacy and ADRs.

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Neurostimulation therapies

Chapter: Neurostimulation therapies

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Electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS) all entail the delivery of electrical energy, either episodically or continuously, to the brain with the object of relieving mental or neurological symptoms. This chapter discusses their indications, application, effectiveness, and safety with respect to depression, and other psychiatric conditions. Because the latter two treatments are relatively novel, the bulk of this chapter is devoted to electroconvulsive therapy.

Electroconvulsive therapy (ECT)

ECT is an effective treatment of severe depression, mania, catatonia, and some cases of schizophrenia. It is important, therefore, that old age psychiatrists have a good understanding of its uses, benefits, and risks. Most researchers have failed to distinguish between older and younger patients in their reports and so much of the evidence presented in this

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chapter is generic in nature and readers must apply the information as best they can to their own practice.

ECT has a multiplicity of actions on the brain. It potentiates the effects of serotonin, noradrenaline, and dopamine; stimulates neurogenesis in animal studies, and blunts pathological hyper-connectivity within cortical and cortico-limbic circuits (Bolwig, 2014; McCall et al., 2014).

Patterns of use

ECT declined in use in most countries from the 1970s onwards, due to the advent of effective antidepressant and antipsychotic medications and to its depiction in popular media as a tool to control aberrant behaviour. Few countries or regions publish complete datasets, but, judging from the number of research publications, ECT and other brain stimulation therapies are in the ascendancy.

ECT is prescribed more per capita to older people than younger ones in Australia (Plakiotis et al., 2012), Denmark (Hundrup et al., 2017), Scotland (NHS National Services Scotland, 2017), the US (Case et al., 2013), and probably most other countries. In Victoria, Australia, where data from all public and private hospitals are collated systematically, applications rose steeply with age until 85 years (Plakiotis et al., 2012) (Fig. 14.1). Likely reasons include an age-related intolerance of antidepressant and antipsychotic medications coupled with an increase with age in depressive psychomotor retardation and psychosis, both of which predict a good response to ECT. It might also reflect a view by psychiatrists that severely depressed old people benefit more from medically oriented therapies. It is conceivable, therefore, that treatment patterns will change yet again now that medications are safer and the role of psychotherapy is expanding.

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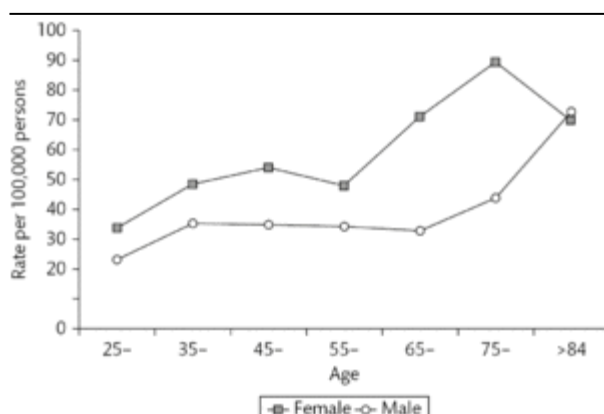


Fig. 14.1

ECT application rates per 100,000 for age- and sex-specific populations in 2007, Victoria, Australia.

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Does ECT work?

Depression

A series of randomized controlled trials (RCTs) in the 1970s and 1980s established that real ECT was superior to sham ‘treatments’ which entailed an anaesthetic but no electrical stimulation. In a meta-analysis of these studies, depressed patients given real ECT improved faster and scored 9.7 fewer points on the 64-point Hamilton Depression Rating Scale (HDRS) two to four weeks later (UK ECT Review Group, 2003).

ECT also proved superior to a range of older and newer antidepressants over periods of 3–12 weeks in all but two of the 13 studies summarized by the UK ECT Review Group (2003). This difference in response translated to 5.2 fewer points on the HDRS. In one of the largest trials, 66% of patients given ECT had no or few symptoms after four weeks compared with 42% of those on imipramine 200 mg daily (Medical Research Council, 1965).

There are remarkably few RCTs of ECT versus other active treatments in older age groups (placebo controls would not be considered acceptable now for very ill people). In the absence of such evidence, naturalistic and between-trial comparisons have some value. In one such report, 78% of depressed people aged 55 years and over (mean age 73 years) had achieved remission (less than ten points on the Montgomery-Åsberg Depression Rating Scale) after a course of mostly unilateral, brief pulse

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ECT (Dols et al., 2017). In another report, 64% of older, severely depressed patients enrolled in a six-week trial of brief versus ultrabrief pulse ECT had achieved remission compared with 33% of similar patients enrolled in a 12-week trial of two antidepressants (Spaans et al., 2015).

Response predictors

Older patients responded better to ECT than younger ones in some studies (Wilkinson et al., 1993; O'Connor et al., 2001) but not in others (Hickie et al., 1996; Birkenhäger et al., 2010). Depressive psychosis and melancholia, as reflected by objective signs of psychomotor agitation and retardation, have strong predictive capacity. In one trial, 75% of patients with psychosis were rated as early responders compared with 22% of those without such symptoms (Spaans et al., 2016). In another trial, the combination of psychotic symptoms with observable psychomotor change was especially potent. Deluded-retarded cases lost 34.7 points on the HDRS in contrast to 16.2 in the retarded, non-deluded group and 10.7 in the non-retarded, non-deluded group (Buchan et al., 1992).

Certain factors reduce, but do not preclude, the likelihood of responding to ECT. These include chronicity and resistance to antidepressant medications (Dombrowski et al., 2005); subcortical hyperintensities (Steffens et al., 2001); medial temporal lobe atrophy (Oudega et al., 2011); and personality disorder (Rasmussen, 2015). Alcohol abuse seemed not to impact on responsiveness in one chart review study (Moss and Vaidya, 2014).

Schizophrenia, mania, and catatonia

All major clinical guidelines accept acute schizophrenia, schizoaffective disorder, mania, and catatonia as possible indications for ECT (American Psychiatric Association, 2001; Royal College of Psychiatrists, 2005; Royal Australian and New Zealand College of Psychiatrists, 2007). Studies and case reports concerning older people with these conditions have been reviewed by Liu and colleagues (2014).

The use of ECT in acute schizophrenia plummeted once antipsychotic medications became available in the 1950s. ECT works a little faster than antipsychotics and is just as effective in reducing psychotic symptoms (Abraham and Kulhara, 1987), but medications are simpler to administer on a long-term basis and are preferred by most patients. Despite recent advances, there remain patients who do not respond to medications, cannot tolerate them, or require urgent intervention to preserve life. In an RCT, 50% of clozapine-resistant patients given ECT showed a 40% or greater reduction in scores on the Clinical Global Impressions scale compared with none in the clozapine only group (Petrides et al., 2015). Old age need not be a barrier to recovery. Kramer (1999) described five women aged 58–74 years whose florid schizophrenia or schizoaffective disorders improved dramatically with ECT.

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In cases of mania, ECT performs as well or better than standard pharmacotherapy (Loo et al., 2011; Versiani et al., 2011). There is little information regarding older patients specifically, but clinical experience suggests that those who cannot tolerate antipsychotic or mood stabilizing medications, or are so manic that they look to be delirious, respond better to ECT. Only small numbers of treatments may be required, even in life-threatening cases of 'delirious mania' (Karmacharya et al., 2008).

Catatonia is now uncommon, but it arises occasionally in schizophrenia, depression, mania, and organic conditions including brain tumour, head trauma, stroke, encephalitis, and metabolic disturbance with any or all of the following signs: mutism, negativism, echolalia, echopraxia, muscle rigidity, posturing, and waxy flexibility. Its severest form, lethal catatonia, is associated with extreme agitation, stupor, fever, sweating, and autonomic instability, leading to dehydration, exhaustion, and death if left untreated. It must be distinguished from neuroleptic malignant syndrome and malignant hyperthermia by means of a reliable medication history. ECT proved effective in 60% of cases after an average of 15 treatments (van Waarde et al., 2010), though maintenance therapy may be required to prevent relapse (Wilkins et al., 2008).

Dementia and other organic mental disorders

ECT is an option when severe depression overlaid on dementia fails to respond to antidepressant medication. Published reports are favourable with improvement rates, however defined, of up to 80% in cases of depression comorbid with Alzheimer's disease, vascular dementia, Lewy body dementia, and frontotemporal dementia (Price and McAllister, 1989; Rao and Lyketsos, 2000; Rasmussen et al., 2003). These reports take the form of small, retrospective case series that are subject to bias: positive reports are more likely to be published than negative ones. To counter this, Nelson and Rosenberg (1991) compared 21 consecutive patients with dementia and comorbid major depression with 84 similarly aged people without dementia. The group with dementia derived almost as much benefit from ECT. While confusion post-ECT was more common and correlated with the degree of dementia, mini-mental state examination (MMSE) scores actually improved on average by 1.6 points. Confusion complicated ECT in half the cases described by Rao and Lyketsos (2000) but it lasted only a few days and treatments continued uneventfully. In one of the few reports to provide follow-up data, relapse rates were high (Rasmussen et al., 2003). With respect to mania in dementia, McDonald and Thompson (2001) described two patients who responded well to ECT in the short term but required ongoing treatment to hold symptoms at bay.

ECT is not a standard treatment of the behavioural symptoms of dementia, e.g. screaming and aggression, that arise in mid- to late-stage dementia, except where patients have comorbid depression and fail to respond to antidepressant medication. Notwithstanding this, 17 case reports with a total of 122 patients described improvement in the

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majority. Adverse effects where present were mostly mild and transient (van den Berg, 2017). In a single prospective series of 23 patients with dementia complicated by agitation or aggression non-responsive to pharmacotherapy, ECT (mostly unilateral) was associated with significant reductions in agitation scores. Where cognitive testing was possible, scores usually improved. Two people failed to respond to treatment and two developed delirium, in part due to unrelated conditions (Acharya et al., 2015). ECT has been delivered safely and effectively to patients with mental disorders secondary to stroke (Currier et al., 1992), Huntington's disease (Ranen et al., 1994), head injury (Kant et al., 1999), and intellectual disability (van Waarde et al., 2001), though relapse rates tend to be high.

Other conditions

ECT can improve tremor, rigidity, bradykinesia, and gait in Parkinson's disease for periods of several weeks, but is rarely used for this indication (Kennedy et al., 2003). It is of greater benefit in neuroleptic malignant syndrome, a condition that overlaps in form with catatonia and is precipitated by antipsychotic medication. Patients who fail to respond to supportive therapy, benzodiazepines, and dopamine agonists, or whose lives are in danger, may benefit from a brief course of ECT. Care is required, however, since patients are often medically unstable (Troller and Sachdev, 1999).

Relapse and maintenance therapy

Relapse is common in the period following ECT. In a study by Sackeim and colleagues (2001), patients whose major depression remitted successfully with ECT were randomly assigned to receive placebo, nortriptyline, or a combination of nortriptyline and lithium carbonate. Over the ensuing 24 weeks, 84% of those on no continuing medication had relapsed, compared with 60% in the nortriptyline group and 39% of those on combination therapy. Relapse was more common in cases resistant to pharmacotherapy. In a naturalistic outcome study, relapse rates were also higher in cases of psychotic depression (31% versus 22%), comorbid psychiatric disorder (43% versus 27%), and personality disorder (23% versus 14%). Relapses were most frequent within two weeks of follow-up (Prudic et al., 2004).

It is now standard practice to introduce an antidepressant medication, either alone or together with an antipsychotic or mood stabilizer, during the ECT course or soon afterwards (Haskett and Loo, 2010). Where medications are known to be ineffective or unsafe, continuation or maintenance ECT is an option. Continuation therapy (C-ECT) follows directly from an acute course of ECT with the object of preventing relapse. Treatment intervals are typically stretched from weekly to monthly depending on progress. Maintenance ECT (M-ECT) refers arbitrarily to treatments extending beyond six months, and occasionally for years, where the risk of relapse is known to be high. Intervals

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between treatments are typically extended until breakthrough symptoms provide clues to the optimal schedule. In an RCT of continuation ECT plus an antidepressant and lithium carbonate versus pharmacotherapy alone, 13% of ECT recipients had relapsed within 24 weeks compared with 20% in the medication only group (Kellner et al., 2016). Outcomes look more promising in longer-term studies. In a retrospective chart review of 58 aged patients with severe, medication-resistant depression or psychosis, hospital readmissions fell by 53% in number and 79% in duration in the two years after M-ECT started compared with the previous two years (O'Connor et al., 2010c). Within the actual M-ECT treatment periods, which varied widely, admissions fell by 90% in number and 97% in duration compared with the same period earlier. Similar findings emerged in earlier reviews of adult patients (Petrides et al., 2011). M-ECT has also been used to limit relapse in bipolar disorder and schizophrenia (Vanelle et al., 1994; Chanpattana et al., 1999).

M-ECT looks to be safe and there is no evidence of progressive cognitive impairment (Rami et al., 2004), even in a patient who received 430 treatments over an eight-year period (Barnes et al., 1997).

Since M-ECT is usually delivered on an outpatient basis, patients must be cooperative, medically stable, and conversant with practical requirements. Processes must also be in place to conduct physical and mental state checks at predetermined intervals, to gauge the intervals between treatments, and to decide when treatment ends (O'Connor et al., 2010b).

Treatment

Anaesthesia

The ideal ECT anaesthetic induction agent ensures rapid, painless unconsciousness, an adequate seizure, and speedy recovery with minimal post-treatment confusion. Methohexital has a rapid onset, short duration of action, and no anticonvulsant properties. By contrast, propofol is sometimes painful on injection and raises seizure thresholds. Its major advantage is that pulse rate, blood pressure, and heart rhythm are more stable (Hooten and Rasmussen, 2008). If seizure threshold is unusually high, or rises steeply as treatment proceeds, or seizure quality is uniformly poor, reducing the dose of propofol may prove helpful, for example, by using augmenting agents like alfentanil or remifentanil (Loo et al., 2010). Other induction agents include etomidate, ketamine, and sevoflurane (Bryson et al., 2017).

Muscle relaxants like succinylcholine virtually eliminate the risk of fractures during ECT, though two cases of vertebral compression fractures were reported by Mulsant and colleagues (1991) in patients known to be osteoporotic. Doses of relaxant can be increased if desired in these situations. Anticholinergics (usually atropine or glycopyrrolate) may be administered just prior to treatment to reduce salivation and

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bradycardia, but only in selected cases given the risks of tachycardia and myocardial ischaemia due to unopposed sympathetic activity (Jadhav et al., 2017).

Seizure threshold

Tonic-clonic seizures are critical to ECT's success (Cronholm and Ottoson, 1960) and the electrical charge must therefore exceed seizure threshold to ensure that a convulsion ensues. Thresholds can vary tenfold or more between patients but lie mostly between 10 and 150 millicoulombs (mC) (Gálvez et al., 2015). Increasing age, male gender, bilateral electrode placement, and propofol anaesthesia all predict higher initial thresholds (Sackeim et al., 1987; Gálvez et al., 2015). Men prescribed bilateral ECT will therefore have higher mean thresholds than women prescribed unilateral ECT.

Electrical charge is not critical in itself. What matters more is that energy levels exceed the threshold by a defined amount. Bilateral ECT is effective at, or just above, seizure threshold. However, unilateral ECT is not, as shown in a critical study by Sackeim and colleagues (2000), in which 'low dose' unilateral treatment (50% above threshold) was much less effective than 'high dose' unilateral treatment (500% above threshold). 'Moderate dose' ECT (150% above threshold) occupied an intermediate position. 'High dose' unilateral ECT worked almost as well as bilateral ECT (50% above threshold) in lifting depressive symptoms.

Stimulus dosing

In former times, the same electrical dose was given to every patient. There is no place for this now: treatments are individualized to maximize efficacy and reduce side effects. There is debate, however, about how best to achieve this. One approach, called stimulus dose titration, entails giving one or more stimulations in the first session to ascertain threshold. A widely used protocol recommends that, for women receiving unilateral ECT, electrical charge is delivered at 32 mC, 48 mC, and then 80 mC until a convulsion is provoked. Once threshold is established, a therapeutic stimulus is delivered at between three times and six times this level (Royal College of Psychiatrists, 1995; American Psychiatric Association, 2001; Mahli et al., 2015). For bilateral ECT, the 'multiplier' is typically one and a half times threshold.

In experienced hands, stimulus titration takes just a few minutes to complete. Inexpert clinicians are less sure-handed, resulting in longer anaesthetics and slower recovery. In earlier decades, repeated subconvulsive stimulations precipitated cardiac arrhythmias but this is rarely seen now. In addition, there is also no evidence that subconvulsive stimulations cause more cognitive impairment (McCall et al., 1994; Prudic et al., 1994).

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Age-based dosing strategies are simpler, faster, and possibly safer for very old, frail patients. According to one formula for unilateral ECT, doses for patients aged 60, 70, and 80 years are about 300 mC, 350 mC, and 400 mC, respectively. Doses for bilateral ECT are half these. According to Tiller and Ingram (2006), age-based dosing led to only 2% of their women patients and 7% of men receiving subtherapeutic doses. Against this, doses would have been too high, at seven or more times threshold, for 30% of women and 8% of men. In addition, if treatment is not progressing well, it is harder to take sensible corrective action if threshold is not known. It is advisable therefore to establish threshold, unless there are good reasons not to do so.

Seizure monitoring

Threshold levels tend to rise as treatment progresses, more for bilateral than unilateral ECT, and electrical charge must be increased to keep pace if this happens (Sackeim et al., 1987). It is not practicable to recheck patients' thresholds week after week. Instead, clinicians make judgments based on EEG monitoring of seizure duration and morphology. This is an imprecise science. ECT machines now produce measures of seizure duration, amplitude, interhemispheric synchronicity and post-seizure electrical suppression, but none of this information can be interpreted exactly.

Greater seizure intensity, regularity and post-seizure suppression correlate with better outcomes (Plakiotis and O'Connor, 2011), but what is cause and what is effect is unclear: patients who respond well to ECT may possess this sort of profile from the outset (Nobler et al., 1993; Perera et al., 2004). A good 'electrical picture' might therefore predict recovery, not cause it. To complicate matters, older people typically have shorter, weaker, and less synchronous seizures, irrespective of clinical outcome, and their thresholds rise faster as treatment progresses (Nobler et al., 1993). In the absence of clear evidence, it seems reasonable to increase electrical charge by 50 mC at a step if seizures become obviously shorter and weaker.

Treatment variants

Efforts continue to boost treatment efficacy while minimizing adverse effects. One alternative to the standard bitemporal electrode placement is bifrontal ECT in which the electrodes are placed 3–5 cm above the outer angle of both orbits. In a recent trial, bitemporal ECT worked a little faster, but the two placements were otherwise indistinguishable (Dunne and McLoughlin, 2012).

In another approach, the standard electrical square wave stimulus is shortened from a pulse width of 0.5–2 milliseconds (ms) to an 'ultrabrief' pulse of 0.3 ms, with the object of depolarizing neurons and stimulating seizures at lower electrical doses. Unilateral ultrabrief pulse ECT is effective and associated with significantly fewer cognitive sequelae than

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standard brief pulse unilateral ECT (Sackeim et al., 2008), but response is a little slower and more treatments are required (Tor et al., 2015). Counterintuitively, bilateral ultrabrief stimuli are strikingly less effective than unilateral ultrabrief stimuli (Sackeim et al., 2008). Ultrabrief pulse treatment has a place for older people with pre-existing cognitive impairment as well as those who became confused after previous courses or who fear post-treatment memory loss.

Some patients have very brief or low-amplitude seizures, and poor clinical outcomes, even at maximal electrical stimulation. Efforts to lengthen and optimize seizures have included hyperoxygenation and pre-treatment with oral or intravenous xanthine alkaloids (caffeine, theophylline, aminophylline). None of these strategies has been subject to rigorous study and xanthine alkaloids can lead to prolonged seizures, tachycardia, and cardiac arrhythmias (Loo et al., 2010).

With respect to frequency, ECT is traditionally administered three times a week, but twice weekly treatments are just as effective (Charlson et al., 2012), require no more treatments in total, and cause less cognitive impairment (Shapira et al., 1998). Barring life-threatening cases, there is no benefit in administering ECT more often.

Concomitant medications

Benzodiazepines raise seizure thresholds and should therefore be avoided, reduced, or stopped if possible but modest doses (e.g. lorazepam up to 3 mg daily) have little impact in reality (Boylan et al., 2000) and are permitted in most ECT research trials to lessen anxiety and agitation. Mood stabilizers that are also anticonvulsants (e.g. carbamazepine and valproate) should also be stopped if possible.

Medications with anticholinergic properties have been linked with worsened cognition post-ECT. Mondimore and colleagues (1983) found that eight of their 12 patients with high serum anticholinergic levels lost two or more points on the MMSE after a single ECT compared with only one of eight patients with lower anticholinergic levels. Tricyclic antidepressants, some antipsychotics, and even lithium carbonate all have discernible anticholinergic activity, as do some analgesics, antihistamines, and antispasmodics (Chew et al., 2008).

Lithium might be hazardous too when combined with ECT, given occasional reports of severe confusion, prolonged seizures, and catatonia, even with 'normal' blood levels (Sartorius et al., 2005). By way of confirmation, rates of confusion were higher at 22% in 27 patients given lithium and ECT concurrently, compared with 12% in those whose lithium was stopped just prior to ECT, and 6% in those with no exposure (Penney et al., 1990). Against this, Dolenc and Rasmussen (2005) cite reports in which lithium and ECT were combined safely. Though the risk of serious mishap is slight, lithium should be stopped if possible before starting ECT.

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Cardiovascular effects

During and immediately after electrical stimulation, an intense parasympathetic surge flows through the vagal nerve to the heart, resulting in a transient sinus bradycardia, with periods of asystole lasting for two seconds on average but occasionally for five seconds or more (Burd and Kettl, 1998). A sympathetic surge then follows, leading to an average rise in blood pressure of 55 mmHg, and in pulse rate of 37 beats per minute, together with clinically benign premature atrial and ventricular contractions. Rare complications at this time include acute myocardial infarction and ventricular fibrillation (Burd and Kettl, 1998). Pulse rates and blood pressure both rise more during bilateral than unilateral ECT, and more with higher than lower energy levels (Gangadhar et al., 2000). Cardiac function usually returns to normal within 15 minutes, but ST changes and arrhythmias (typically bursts of bigeminy or trigeminy) are a little more common than usual in the following 24 hours (Huuhka et al., 2003).

Safety

In an analysis of nearly a million treatments in 32 countries, the mortality rate associated with ECT was 2.1 per 100,000 treatments, with a decline in the last decade (Tørring et al., 2017), placing the risk at the bottom of the range for procedures requiring general anaesthesia (Watts et al., 2011). This is not because treatment is reserved for physically fit patients. ECT is given quite commonly to patients with serious medical comorbidities compounded by dehydration, inanition, and exhaustion secondary to depression or psychosis. It might actually be safer than psychotropic medications in such circumstances. In a chart review by Zielinski and colleagues (1993), 11 of 21 patients with cardiac disease were forced to discontinue treatment with tricyclic antidepressants because of cardiovascular complications compared with only two of 40 comparable patients given ECT. Similarly, cardiovascular and gastrointestinal (GI) complaints were more common in 39 very old, pharmacologically treated depressives compared with 39 carefully matched patients treated with ECT (Manly et al., 2000). There are risks, however, as the following sections make clear.

Aged patients are at higher risk of adverse events. In a report by Burke and colleagues (1987), 15% of patients aged 60 years and over experienced a cardiorespiratory complication (mostly changes in blood pressure) compared with 3% of younger patients, and 15% sustained a fall versus none in the younger group. Rates of post-ECT confusion were 18% and 13%, respectively. Altogether, 35% of older patients had a complication, but most were transient and settled spontaneously. Side effects also rose with age in a chart review by Alexopoulos and colleagues (1984). Cardiovascular complications arose in 19% of patients aged 65 years and over versus 1% of younger patients, and 14% had neurological complications (mostly confusion) compared with 12%. Apart from an 87-

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year-old man who died of a myocardial infarction 48 hours after his second treatment, most patients went on to complete their course.

Cattan and colleagues (1990) found that octogenarians had adverse events roughly twice as often as 'younger old' patients. Cardiovascular complications and falls were more frequent in very old patients than younger ones at 36% versus 12%, and 36% versus 14%, respectively. Confusion was the commonest problem, arising in 59% and 45% of the two groups. Outcomes were more benign in the patients aged 75 years and over described by Gormley and colleagues (1998), of whom 7% suffered prolonged confusion and 4% became manic. All problems resolved within two weeks. Similarly, Tomac and colleagues (1997) reported that 32% of the patients aged 85 years and over experienced prolonged confusion and 10% fell. One of the 34 patients sustained a fracture between treatments and six died of causes unrelated to ECT within 45 days after the last treatment, attesting to their very high rates of physical comorbidity.

Other uncommon side effects include dental injury, fractures secondary to falls (de Carle and Kohn, 2001), and vertebral compression fractures due to poorly modified seizures (Mulsant et al., 1991). Very rare sequelae include stroke (Bruce et al., 2006) and status epilepticus (Srzych and Turbott, 2000). Neurological asymmetries are common after ECT but generally resolve within 20 minutes (Kriss et al., 1978).

Prevention and management

Contraindications to ECT include recent myocardial infarction and stroke, severe valvular heart disease, clinically significant arrhythmias, unstable angina, uncompensated cardiac failure, and cardiac and arterial aneurysms, but these rules are not absolute. ECT has been applied safely and effectively in patients with recent myocardial infarction (Magid et al., 2005), cardiomyopathy (Adabag et al., 2008), aortic aneurysm (Mueller et al., 2009), pulmonary embolism (Suzuki et al., 2008), cerebral aneurysms and angiomas (Kang and Passmore, 2004), and a wide range of neurological conditions (Ducharme et al., 2015).

Examples of the strategies required to minimize risk in medically compromised patients are described by Tess and Smetana (2009). These include pre-treatment with atropine or glycopyrrolate to prevent bradycardia (though atropine may worsen post-ECT confusion); pre-treatment with betablockers to limit hypertension and tachycardia (though unopposed parasympathetic activity can worsen bradycardia); reductions in anticoagulant therapy for patients with an intracranial mass or aneurysm; and additional muscle relaxation for those with fractures or marked osteoporosis. A careful physical examination, ECG, measures of renal function, and discussions with medical and anaesthetic colleagues are vital. Other laboratory and imaging results add little extra information

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(Lafferty et al., 2001). Implanted cardiac pacemakers present no special risk (Dolenc et al., 2004).

Cognition

Objective changes

No evidence has emerged from numerous anatomical and imaging studies that ECT causes altered brain structure, neuronal death, or cerebral atrophy (Devanand et al., 1994; Ende et al., 2000). There is no doubt, however, that ECT can result in objective cognitive disruption. Patients are sometimes confused and disoriented on waking from anaesthesia. This typically lasts just for a few minutes but extends occasionally for hours and rarely for several days. Risk factors for emergent confusion include bilateral electrode placement (Sackeim et al., 1993); high electrical dose relative to threshold (Sackeim et al., 1993); a sinusoidal waveform (Daniel and Crovitz, 1986); advanced age (Tomic et al., 1997); pre-existing dementia (Rao and Lyketsos, 2000); and concomitant anticholinergic medications (Mondimore et al., 1983).

Most studies show some reduction in the acquisition and retention of new verbal and nonverbal material (anterograde memory) over the course of a treatment cycle. Improvement starts within a few days of treatment completion, more quickly for information acquisition than retention, and continues for up to six months. Recall of past events (retrograde memory) is also affected, especially for personal or autobiographical memories, and for recent events more than distant ones (Ingram et al., 2008). Autobiographical memory is difficult to measure in a standardized way and so the nature, extent, and duration of lapses is unclear. Knowledge of events in the days or weeks prior to treatment may never be recovered, extending in some cases to a more than a year beforehand (Ingram et al., 2008).

Risk factors for anterograde and retrograde amnesia include bilateral electrode placement (Sackeim et al., 2000), high electrical dose relative to threshold (Sackeim et al., 2000), advanced age (Zervas et al., 1993), and limited education (Legendre et al., 2003). Impaired cognition at baseline and prolonged disorientation after treatment are associated with a heightened risk of retrograde amnesia (Sobin et al., 1995). Other risk factors include substance abuse, cardiac disease, and neurological disorders (Sackeim, 2000).

Remarkably few studies have focused on old people, despite their higher rates of premorbid cognitive impairment, and most were small and of poor quality. Post-treatment confusion is certainly more common and cognition typically declines as treatment progresses, more for bilateral than unilateral ECT (O'Connor et al., 2010a), but recovery is usually rapid (Russ et al., 1990; Rubin et al., 1993). Published reports may not be fully representative of clinical experience, however, since many severely depressed patients cannot participate in cognitive testing or consent to

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research. The patients who are most vulnerable to cognitive side effects might therefore be excluded from study (Gardner and O'Connor, 2008).

In the longer term, some cases of dementia must be expected in older age groups because of the established links between depression, on the one hand, and incipient cerebrovascular and Alzheimer's diseases, on the other. While rates look high at 14% in the patients aged 65+ years who were followed for three years by Godber and colleagues (1987) and 36% in those aged 75+ years followed for five years by Brodaty and colleagues (2000), there is no reason to believe that ECT plays a causative role.

Clinical guidelines highlight the need for cognitive assessment before, during, and after an ECT course but leave the choice of tests to the clinician (American Psychiatric Association, 2001; Royal College of Psychiatrists, 2005). Porter and colleagues (2008) proposed using the MMSE as a baseline measure; checking time to reorientation in the recovery room after every treatment; a brief test of verbal learning after every third treatment; and an abbreviated autobiographical memory questionnaire after every sixth treatment. All these tests can be administered by a trained nurse.

Cognitive impairment is prevented or minimized by administering ultrabrief pulse unilateral ECT in the first instance, titrating stimulus intensity, prescribing only two treatments each week, and limiting the number of treatments in a course, subject to clinical progress (Prudic, 2008; Mayur et al., 2013). There is some evidence that cholinesterase inhibitors might also prove helpful (Henstra et al., 2017).

Subjective reports

While complaints of poor memory subside as depression remits (McCall et al., 1995; Coleman et al., 1996), between 29% and 88% of patients describe some persistent forgetfulness in coming weeks and months (Brodaty et al., 2001; Rose et al., 2003; Philpot et al., 2004). Gaps in memory of the six months before treatment and the two months afterwards are common and mostly well tolerated (Freeman et al., 1980). Of more concern to patients are 'holes' in past memories and difficulties with remembering faces, names, and lists (Freeman et al., 1980). Risk factors for subjective deficits include bilateral electrode placement and high electrical charge (Squire and Slater, 1983; Coleman et al., 1996).

Mood also plays a role. Patients whose depression persists despite treatment tend to report greater memory difficulties and to perceive ECT more negatively (Freeman and Kendall, 1980; Coleman et al., 1996). This is not surprising: mood correlates strongly with self-rated memory, even in community populations (O'Connor et al., 1990).

Self-perceived cognitive changes, when assessed using standard questionnaires, are only weakly associated with scores on objective tests, perhaps because the questionnaires fail to tap patients' personal memories. In fact, responses to a single, general question about memory

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changes correlate quite well with objective performance, suggesting that complaints have validity (Brakemeier et al., 2011).

Previously, psychiatrists tended to blame complaints on patients' ongoing psychopathology, their loss of self-efficacy, or excessive concern with normal cognitive changes (Prudic et al., 2000). Others were more circumspect. Freeman and colleagues (1980) noted that ECT 'complainers' were only fractionally more depressed on mood rating scales than 'noncomplainers'. Following from this, and from the observation that the temporal gradient in complaints fitted better with ECT than depression as causative agent, Sackeim (2000) concluded that 'attributing these subjective deficits to ongoing psychopathology or natural disease progression would seem disingenuous and defensive'. An account by one patient is especially compelling. Donahue (2000) wrote that ECT (initially unilateral and then bilateral) saved her from suicide. She felt grateful to be alive and would have ECT again if necessary, but whole chunks of her life had been lost to her—a cost she accepted but could not deny.

Ethical issues

For patients with the capacity to consent, ECT should be administered only with their agreement. Consent must be voluntary, based on an adequate explanation of the nature of ECT, its practical implications and side effects, tailored to individual circumstances. Patients concerned about cardiac symptoms, for example, need more detailed information about cardiovascular sequelae. Verbal discussion is best supplemented by an informational brochure that patients and families can digest at leisure, modelled perhaps on the document prepared by the American Psychiatric Association (2001). Moderately depressed, cognitively intact older patients absorb and retain this sort of information quite adequately (Lapid et al., 2004). A visit to the ECT treatment suite to explain its procedures and equipment can allay patients' and relatives' concerns.

Clinicians will naturally advocate for ECT when its use is warranted. There is a fine line, however, between persuasion and coercion. Patients' apprehension typically settles with appropriate reassurance and factual responses to questions, but doctors and patients sometimes perceive this process differently (McCall, 2006). In a review of 17 reports Rose and colleagues (2003) reported that only half the respondents believed they had been given an adequate explanation of ECT and most had limited knowledge of actual procedures. Patients sometimes recounted giving 'consent' while heavily sedated or threatened by legal compulsion. These recollections might sometimes be inaccurate, but patients are left traumatized as a result. Johnstone (1999) described the perceptions of shame and despair by 20 aggrieved ECT recipients; it is required reading for clinicians.

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Some of the patients most likely to benefit from ECT are unable to consent by virtue of marked depression or psychosis. Pointers to lack of capacity include difficulty recalling basic information about the nature and consequences of ECT, marked difficulty in decision-making, delusional nihilism about the prospects of recovery, and an inability to speak. Treatment can be applied in most jurisdictions on an involuntary basis with review by a court or tribunal. It is important to document the reasons for mandating ECT; the pros and cons of alternative treatments; patients' mental state and capacity to make informed decisions; and family viewpoints. Except in emergencies, second opinions are encouraged. The limited research conducted to date suggests that nonconsenting patients often rate their outcome as satisfactory (Wheeldon et al., 1999). Patients who accept ECT passively but cannot contribute to the decision-making process are best treated involuntarily to ensure legal oversight and protection (Law-Min and Stephens, 2006).

ECT typically entails a series of treatments over a period of weeks. Mental capacity will often improve as depression or psychosis abate, with the result that noncompetent patients become competent and can participate in the decision to continue with treatment. Conversely, a patient made confused by ECT may lose competence for a period of time. Ethical practice requires a constant monitoring of patients' mental states, attitudes to ECT, and decisional capacity. Repeated explanations of the reasons for administering ECT and its likely benefits and side effects may be required if patients fail to recall initial discussions.

Attitudes to ECT

Patients' views

Fear of ECT is widespread. In a survey of 56 Australian general hospital visitors, none of whom had received ECT, many agreed that it ablated memory and rendered patients 'zombies' (Kerr et al., 1982). Psychiatrists attribute this fear to misinformation spread by popular movies and lobby groups, but, in reality, a dread of electricity is instilled in children from an early age.

Malcolm (1989) detailed the concerns expressed by 100 patients prior to ECT. Their fears included brain damage, memory loss, pain, being seen by strangers while unconscious, having a heart attack, and developing epilepsy. Their knowledge of ECT was rudimentary: only 16% knew that a convulsion was induced and many expected a single treatment. Older people were more stoical: 52% denied fear compared with 30% of younger ones. When the same patients were asked later what aspects most perturbed them, they nominated waiting for treatment, seeing equipment laid out, hearing staff talk in the background, breathing into an anaesthetic mask, and waking up afterwards.

In a retrospective survey, only 6% of 70 British patients who had received ECT rated it as much worse than a visit to the dentist (Benbow and

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Crentsil, 2004). By contrast, 7% of Australian patients said that they dreaded it and another 12% found it frightening (Kerr et al., 1982). Occasionally patients develop an overwhelming horror of ECT, usually after lengthy or repeated courses (Fox, 1993).

Not all patients are negatively disposed. A psychiatrist who received ECT himself described a lifting of mood after the first treatment. Side effects—nausea, stiffness of the jaw, topographic disorientation, and mild memory loss—were a small price to pay in his view (Vallance, 1965). Another patient, while grateful for treatment, described the stigma and inconvenience of maintenance ECT (Hensley, 2008).

Patients' views are coloured in part by their mental status. Depression brings with it fears of therapeutic nihilism. As these fears remit with treatment, opinions of ECT may become more positive (Chakrabarti et al., 2010). Favourable views post-ECT correlate with the severity of mental disorder and disability pre-ECT, fewer treatment side effects, and a perception of good care while in hospital, but not with legal status (Wheeldon et al., 1999; Philpot et al., 2004; Rosenquist et al., 2006). This suggests that the sickest patients, who stand to derive the greatest benefit from ECT, come to perceive it most favourably.

In a meta-analysis of 16 published reports, positive views of ECT emerged most commonly from studies conducted shortly after ECT by psychiatrists using brief checklists. Studies conducted by independent investigators some time after admission using open-ended questions were less encouraging (Rose et al., 2003). This suggests that structured assessments conducted by doctors in medical environments may fail to tap patients' true perceptions.

Proposed strategies to improve acceptance of ECT include educational videos, use of ECT-experienced peer support workers, minimizing time in the waiting room, and reducing exposure to technical paraphernalia (Westreich et al., 1995; Koopowitz et al., 2003; Parvin et al., 2004). The video deployed in one study made no discernible difference to patients' knowledge, perhaps because they were too depressed to benefit, but it was greatly appreciated by families, whose support is often critical (Westreich et al., 1995).

Families' views

Little research has been conducted of family members' attitudes to ECT, both before and after treatment. This is a deficiency, since an informed, positively disposed family can do much to assist patients through their illness and treatment. In the meantime, two compelling accounts have been published of relatives' battles with sceptical psychiatrists to secure ECT for a father and son respectively whose mental disorders had failed to respond to medications and psychotherapy. Their efforts were rewarded by excellent clinical outcomes (D'Agostino, 1975; A Grateful Parent, 2005).

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Practice standards and training

Variations in practice

ECT can work quickly and effectively when administered by skilled clinicians to carefully selected patients. In a large, prospective North American study of suprathreshold bilateral ECT, 75% of patients had remitted after seven sessions as shown by HDRS scores of 10 or less (Husain et al., 2004). The same might not apply, though, when patients with complex, chronic conditions are treated in mainstream facilities using suboptimal methods. As an example, in a survey of hospitals in New York state where treatment practices varied widely, HDRS scores fell below 10 points in only 47% of all cases. To make matters worse, 40% of accrued improvement was lost within ten days and relapse rates ranged from 46% to 79% across sites (Prudic et al., 2004).

In a related study the investigators were perturbed to find that 17% of 59 mental health facilities administered the same electrical charge to all patients; 8% of facilities failed to monitor seizure duration; and 20% neglected to check patients' cognitive status. Such a wide variability in how ECT is conducted raises serious public health concerns (Prudic et al., 2001).

Training deficiencies were commonplace until recently. Of 160 junior doctors in England and Wales, 63% had watched an instructional video but only 53% had been supervised by an experienced psychiatrist when giving their first treatment and only 4% were routinely supervised thereafter (Duffett and Lelliott, 1998). Similar findings emerged in New South Wales, Australia, where 20% of doctors were not supervised in their first session by another medical practitioner (Halliday and Johnson, 1995).

Clinical guidelines

Three national professional bodies have since published detailed accounts of ECT's indications and contraindications; proper assessment and treatment procedures; legal and ethical standards; and training and supervision requirements (American Psychiatric Association, 2001; Royal College of Psychiatrists, 2005; Royal Australian and New Zealand College of Psychiatrists, 2007). The American Psychiatric Association stipulates that trainee psychiatrists should complete at least 10 treatments under direct supervision and then attend regular ECT review meetings. 'Privileging' to administer ECT independently requires objective evidence of safe, proficient practice that conforms to local standards. Further education might include attendance at an ECT course, a structured clinical practicum, supervised reading, and participation in quality assurance activities.

A checklist prepared by the Royal College of Psychiatrists' Research Unit (2006) of basic, standard, and ideal policies and procedures covering all aspects of physical facilities, staff training, patient assessment and

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treatment, consent, and follow-up provides a template for self-appraisal in any ECT service. A curriculum for psychiatry trainees has been proposed by Dolenc and Philbrick (2007) that covers all important areas of theory and clinical application.

Transcranial magnetic stimulation

Repetitive TMS uses a pulsed magnetic field to induce an electrical current in the underlying cerebrum, targeting the neural circuitry implicated in depression and possibly other conditions including auditory hallucinations, obsessive-compulsive disorder (OCD), substance use disorder, and post-traumatic stress disorder.

The magnetic pulses used in TMS are of comparable strength to those used in magnetic resonance imaging. Rapid pulses (5 Hz and above) increase the activity of the underlying cortex while slower pulse rates (1 Hz and below) reduce activity. In a newer development, theta-burst stimulation, very high frequency stimulation is repeated in 'bursts' at a frequency in the theta range (Chung et al., 2015).

During TMS, patients sit in a purpose-built chair with the coil positioned over the scalp. The commonest coil is a figure-of eight design, though other configurations exist. The usual strategy is to administer brief pulses over the primary motor cortex to determine the minimum amount of power required to make the thumb twitch (the motor threshold). For treatment of depression, the coil is typically positioned to deliver high frequency stimulation to the left dorsolateral prefrontal cortex (DLPFC). If this proves ineffective, an option is to direct low frequency stimulation to the right DLPFC. Treatments typically take 20 to 40 minutes on five days per week over four to six weeks depending on clinical progress. As no sedation is required, normal activities can be resumed immediately (George and Aston-Jones, 2010).

Objects affected by magnetic fields (e.g. deep-brain stimulators, cochlear implants, and metal objects in the eye) present an absolute contraindication to TMS as they can move or become heated. Implants such as aneurysm clips that are manufactured to be 'MRI compatible' are considered safe. Advice should be sought if in doubt. TMS is relatively contraindicated in patients with a history of seizures or with conditions that lower the seizure threshold (e.g. disseminated sclerosis or recent cortical bleeds or infarctions).

Side effects are generally transient and mild (Rossi et al., 2009). About 40% of patients experience a degree of local discomfort or headache. Hearing protectors reduce the risk of hearing loss from the coil's noise.

TMS has proven antidepressant effectiveness. A recent review found evidence of definite efficacy for left, high frequency DLPFC stimulation and probable efficacy for right, low frequency DLPFC stimulation (Lefaucher et al., 2014).

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TMS appears to be as effective in older as in younger adults (Conelea et al., 2017). In an open-label study of left DLPFC TMS in 65 older, treatment-resistant patients, 58% showed a 50% or greater reduction in HDRS scores (Sayar et al., 2013).

In a meta-analysis of 25 studies of major depressive disorder (MDD), Chen and colleagues (2017) reported that the cumulative probabilities of being the most efficacious treatment were: ECT 65%; bilateral DLPFC TMS 25%; right DLPFC TMS 8%; and left DLPFC TMS 2%. The cumulative probabilities of being the best-tolerated treatment were: right DLPFC TMS 52%; bilateral DLPFC TMS 17%; left DLPFC TMS 16%; and ECT 14%. Notwithstanding these findings, the time and expense associated with TMS limits its utility as a first-line treatment.

Preliminary evidence exists that TMS can improve performance on several of the cognitive functions impaired in mild cognitive impairment and Alzheimer's disease (Nardone et al., 2014). Other areas for research include new forms of coils and magnetic field geometry, and better individual tailoring of treatment procedures (Lefaucher et al., 2014).

Deep brain stimulation

DBS has generated interest as a psychiatric treatment modality following its success in treating neurological disorders such as Parkinson's disease, epilepsy, and chronic pain. It involves the precise bilateral implantation of electrodes in deep brain nuclei via stereotactic neurosurgery and their connection to an implantable pulse generator situated in the chest wall. The electrodes deliver continuous high-frequency stimulation to the surgical target using parameters (pulse frequency and width, stimulation intensity, and the size and shape of the stimulation field) that can be adjusted non-invasively (Mosley et al., 2015; Fitzgerald and Segrave, 2015).

The mechanisms of action of DBS remain speculative but, in contrast to psychosurgery, most probably involve functional alterations in brain activity rather than disruption of specific brain regions (Fitzgerald and Segrave, 2015). The neuronal effects of DBS are both inhibitory and excitatory in nature, depending on the location and mix of cell bodies and white matter fibres in the stimulated field, as well as the stimulus parameters themselves (Holtzheimer and Mayberg, 2011). At a systems level, DBS is presumed to act on cortico-striatal-thalamic-cortical neural circuits implicated in conditions like depression and OCD (Ward et al., 2010).

Studies of DBS for psychiatric disorders are limited in size but the results look promising. Naesström and colleagues (2016) systematically reviewed the indications for DBS in treating psychiatric illness, particularly major depressive disorder (nine studies with 100 patients) and OCD (18 studies with 112 patients). In the largest depression study involving 21 patients who received subcallosal cingulate gyrus stimulation, response rates

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were 57% at one month, 48% at six months, and 29% at 12 months, where response was defined as a 50% or greater reduction in the 17-item HDRS score (Lozano et al., 2012). However, the 12-month response rate increased to 62% when defined as a 40% or greater reduction in the HDRS score. In the largest study of OCD, the long-term results of ventral internal capsule/ventral striatum stimulation showed clinically significant symptom reduction and functional improvement in about two-thirds of the 26 patients. Results improved over time as the target area was moved more posteriorly, to the junction of the anterior capsule, anterior commissure, and posterior ventral striatum, based on outcome appraisal (Greenberg et al., 2010). Other disorders addressed in the systematic review, usually with very small numbers of studies, included Tourette's syndrome, anorexia nervosa, heroin addiction, alcohol addiction, agoraphobia with panic attacks, and autism (Naesström et al., 2016).

DBS is invasive and its adverse effects include perioperative complications (haemorrhage, seizures, and death); hardware-related complications (infection, electrode misplacement, and skin erosion), and target- and patient-specific side effects of stimulation (transient memory impairment, musculoskeletal and GI complaints, agitation, and irritability) (Neumaier et al., 2017). Unlike lesional psychosurgery, however, DBS is reversible, produces minimal tissue destruction, and is easily adjusted or switched off. Clarification of optimal stimulus targets, treatment profiles, patient selection criteria, and long-term outcomes are future research directions (Fitzgerald, 2011). Patients with melancholic depression who respond to ECT but continuously relapse with maintenance psychotherapy, pharmacotherapy, or TMS may be ideal candidates for future DBS trials (Mosley et al., 2015).

Conclusion

- ECT is an effective, accepted treatment of depression. It works faster, and may be safer than pharmacotherapy for frail, older patients but relapse rates are high once treatment stops. Continuing pharmacotherapy is mandatory. ECT works best in depressed patients with psychomotor changes and psychotic symptoms.
- There is a place for ECT in medication-refractory cases of mania, acute schizophrenia, and catatonia.
- Electrical stimulation must always exceed seizure threshold, more for unilateral than bilateral ECT. Stimulus titration ensures that energy charges are individualized. Fixed-dose, high-energy treatments are not acceptable.
- Very old patients have higher rates of cardiovascular complications, confusion, and falls. Twice-weekly ECT is adequate. Benzodiazepines, anticonvulsants, and medications with anticholinergic properties should be stopped if possible.
- Complaints of memory loss abate with time, but gaps in memory may persist.

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- Capacity to consent to ECT can change as treatment progresses and explanations may need to be repeated. Educational brochures and videos are encouraged.
- ECT is perceived negatively by many patients and families and great efforts must be made to address their concerns accurately and to reduce the risk of poor outcomes.
- Such a complex treatment should never be administered by untrained staff.
- Few published reports focus just on frail, aged patients. Further research is required to ensure that treatment of this vulnerable group is made as safe and effective as possible.
- TMS is better tolerated, but less effective, than ECT as a treatment of major depression.
- DBS requires major surgery and its role is limited to the treatment of severe, chronic, and disabling psychiatric disorders.

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Person- and relationship-centred dementia care: Past, present, and future

Chapter:

Person- and relationship-centred dementia care: Past, present, and future

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Introduction

It has been recognized for some time that supporting people with dementia and their family carers represents the most significant challenge facing health and social care systems throughout the world over the next 50 years (Jennings, 1999). However, debates as to the best model and care pathway to adopt continue to evolve, with various approaches to the support of people with dementia and their family carers being advocated. For instance, during the last 40 years or so, services and professional attitudes have moved from a largely deficit-based model focusing on the person-with-*dementia* through to a much more personalized, individualized, and self-deterministic approach with an emphasis on the *person-with-dementia* (Kitwood, 1997; 7), a momentum which, in England, culminated in the publication of the

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National Dementia Declaration (Dementia Action Alliance, 2010). The Declaration involved people with dementia in all stages of its development and composition. Indeed, its goal was to change the experience of living with dementia in England 'for good', a process that was framed through seven 'I-statements' aimed directly at people with dementia, e.g. 'I have personal choice and control or influence over decisions about me' and 'I have a sense of belonging and of being a valued part of family, community and civic life.' More recently, and with the support of the Alzheimer's Society, these seven 'I-statements' were refreshed and relaunched by people with dementia (Dementia Action Alliance, 2017) and now comprise five statements about the collective rights of people living with dementia (Box 15.1).

Box 15.1 The dementia statements

- We have the right to be recognised as who we are, to make choices about our lives including taking risks, and to contribute to society. Our diagnosis should not define us, nor should we be ashamed of it.
- We have the right to continue with day-to-day and family life, without discrimination or unfair cost, to be accepted and included in our communities and not live in isolation or loneliness.
- We have the right to an early and accurate diagnosis, and to receive evidence based, appropriate, compassionate and properly funded care and treatment, from trained people who understand us and how dementia affects us. This must meet our needs, wherever we live.
- We have the right to be respected, and recognised as partners in care, provided with education, support, services, and training which enables us to plan and make decisions about the future.
- We have the right to know about and decide if we want to be involved in research that looks at cause, cure and care for dementia and be supported to take part.

Reproduced with permission from National Dementia Action Alliance (2017). Dementia Statements. Available on line at: <https://nationaldementiaaction.org.uk/dementia-statements/>, accessed 02nd September 2019.

The Dementia Action Alliance suggests that these five new dementia statements replicate the things that people with dementia believe are essential to their quality of life and exist to act as a rallying call to improve the lives of all people with dementia. Changing 'I' to 'We' in this new set of statements also promotes a more inclusive and shared vision/

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experience of living with a dementia. Arguably, these five new dementia statements also act as a mirror to society to reflect the changes in public and policy perception about the condition in the UK, a change that has been propelled through increased public awareness (e.g. via the Dementia Friends initiative: <https://www.dementiafriends.org.uk/>; accessed 29 January 2018) and embedded in dementia-friendly social policy architecture. This latter change is seen most clearly in the targets and implementation plans attached to the development of dementia-friendly communities in the UK and set out in the Prime Minister's Challenge on Dementia 2020 (see, for example: Department of Health, 2012, 2015, 2016).

Recent times have also seen the emergence of relational and dynamic models that transcend the essentially individualistic approach of person-centred care (Post, 2001) and take a triadic perspective with a focus on the relationships and interactions between people with dementia, their family carers, and formal service systems (Nolan et al., 2002b; 2006). Such trends reflect both advances in thinking about the nature of the 'dementia experience' and the importance now accorded to the active engagement of users, carers, and professionals. This approach recognizes that each of these partners is an 'expert' in their own right and that a complete understanding will only emerge when these differing, but complementary, perspectives are brought together (Nolan et al., 2007). The approach also acknowledges the growing importance attached to enabling people with dementia to be more active in the conduct and practice of research attached to their own lived experience so that the power relationships between users, carers, and professionals are harmonized as far as this is both practical and possible to achieve (for an example of people with dementia acting in a co-research capacity alongside academic researchers, see Swarbrick and Open Doors, 2017). Nowadays, and as highlighted previously in the five new dementia statements, such a push for harmonization is being taken forward by people with dementia themselves as a fundamental right and positioned through the language of equality and equity (Mental Health Foundation, 2015; Dementia Alliance International, 2016; The Race Equality Foundation, 2016). The times are undoubtedly changing.

This chapter presents a historical overview of the above changes and then focuses on a particular approach to working with people with dementia, family carers, and paid carers based on the concept of relationship-centred care (Tresolini and the Pew Fetzner Task Force, 1994) as captured in the 'Senses Framework' (Nolan, 1997; Nolan et al., 2002a,b, 2006). It begins with a brief review of some of the key considerations in dementia before charting the rise of person-centred and relational models. It then presents a more detailed consideration of the conceptual and empirical bases for the 'Senses Framework', followed by a case study that illustrates its practical application. The chapter concludes with a glance towards the future and proposes that relationship-centred care could extend its triadic structure by adding a fourth domain: the informal,

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community-based social networks of people with dementia and their families as they live their lives 'outside their front door' in the everyday community spaces and resources that exist in the local neighbourhood. Ward and colleagues (2017) recently argued that accounting for, respecting, and authenticating the relationships that people with dementia and their families have with neighbours, the neighbourhood at large, shops, friends, and where 'life is lived everyday' are important social world dimensions now receiving attention in the literature and in policy formation.

Dementia: Key considerations

Currently, there are no restorative cures for any of the dementias and promoting, and adopting a healthy lifestyle is presently advocated as the main option for treatment (Alzheimer's Disease International, 2016). Education and skills training for health and care staff who are engaged in the support and care of people living with dementia are therefore recognized as crucial for high-quality compassionate and culturally competent care to emerge (Department of Health, 2016). A review of psychological interventions for carers of people living with dementia by Elvish and colleagues (2012) found that multicomponent interventions were among the most effective, and interventions underpinned by cognitive/cognitive behavioural models appeared to produce meaningful change. A narrative review by Roach and colleagues (2009) on the experience of living with young-onset dementia highlighted the importance of dedicated service provision for this group. They also found that age, employability, current family composition, and presentation of symptoms related to dementia combine to significantly raise the stress for individuals and their families, especially when teenage children are present in the home. This intergenerational impact of the lived experience of dementia is a timely reminder that 'dementia' extends beyond the traditional 'dyad', however that relationship is defined, and reaches out to other members of the family (Roach et al., 2014; Koo and Pusey, 2017). The impact also extends to the wider neighbourhood and the home where people with dementia live, a space that includes the garden (where there is one) and those spaces around the home that bring people with dementia into contact with the outside world (Ward et al., 2017).

Recognition that dementia is not confined to later life is also a timely reminder of the history of the condition and the work of the German psychiatrist and neuropathologist Dr Alois Alzheimer, from whom the disease takes its name. In November 1901, at the age of 51, Auguste Deter was admitted to the Frankfurt am Main insane asylum at the behest of her husband. The family doctor's admission note from 1901 survives, and it shows that Mrs Deter's condition required 'treatment' from the local asylum as she was experiencing weakening of the memory; persecution mania; sleeplessness; restlessness; and an inability to perform any physical or mental work (Maurer and Maurer, 2003). Dr Alzheimer himself performed various cognitive, psychological, and

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dexterity tests at the time of Mrs Deter's admission, which included an appraisal of her reading and writing performance. For example, Alzheimer recorded Mrs Deter's performance in the following way (Maurer et al., 1997):

... when she has to write Mrs Auguste Deter, she writes Mrs and we must repeat the other words because she forgets them. The patient is not able to progress in writing and repeats, 'I have lost myself' (p. 1548).

After Auguste Deter's death in the asylum on 8 April 1906, it was the staining techniques applied to her brain by Alzheimer and his colleagues that identified the amyloid plaques and neurofibrillary tangles that, to this day, remain confirmatory biological markers for presence of the disease and gave rise to the description of the 'clinical symptoms' of 'presenile dementia' (Maurer and Maurer, 2003). The search to further understand the biological functioning of the brain, and the death/dysfunction of the responsible neurotransmitters, largely marked Alzheimer's disease as 'medical territory' for much of the twentieth century with its diagnostic classification, and that of 'dementia', written into international mental health disease classifications (e.g. World Health Organization, 1992, 2016).

Arguably, the direct alignment between 'Alzheimer's disease' and 'mental health/illness' promoted a deficit-based model and further exposed those living with the condition to the stigma of mental illness, as well as to the stigma of ageing. Indeed, closer inspection of the quotation above reveals the 'malignant positioning' (Sabat, 2001, 2002) by Alzheimer of Auguste Deter as 'a patient' [rather than as 'a person'] and an inmate of the confining and austere environment of the Frankfurt am Main insane asylum. In such a setting, opportunities for individual expression and self-determination would have been limited, to say the least.

Similarly, the subsequent focus on the 'staining technique' on her deceased brain, rather than attempting to find meaning in Auguste Deter's profoundly self-aware words of 'I have lost myself', effectively closed the door on what is now central to dementia care practice—namely the use of life story work (Kellest et al., 2010; McKeown et al., 2010, 2015; Gridley et al., 2016). Auguste Deter's life story did not emerge until 100 years after her death when Page and Fletcher (2006) pieced together the fragments of her life that they were able to recover from various sources. In the story that emerged, Mrs Deter was not simply 'a patient' whose brain gave life to Alzheimer's disease, but until the time of her death at the age of 56, she remained a married woman who had had a daughter called Thekla. As Page and Fletcher (2006) reveal, Auguste Deter married Karl, a railway clerk, when she was 23 years of age and it was at this time in the young couple's life that they moved to Frankfurt to continue their life from within the protestant religion. It was also reported that after his wife's admission to the asylum in 1901, Karl Deter struggled to pay the fees for his wife's care and he was seen to visit her

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'frequently'. Rather movingly, Mrs Deter is described in the admission notes as being a 'tall woman with long brown hair, brown eyes and elegantly long fingers' (Page and Fletcher, 2006; 578), and as far as it can be ascertained from the available writings, she was a woman who had a preserved sense of identity—in the eyes of her husband and daughter—as a wife and as a mother.

We would like to think that Auguste Deter had a sense of belonging and significance for those who loved her, but defining people with dementia from within their own relationships, life story, and preserved attributes was not the dominant narrative of the early twentieth century. This discourse was not to change until society began to question the morality and ethical standpoint of institutional and asylum-based care, and influential academics, practitioners, and policy makers began to challenge the long-held assumption that living with dementia equated simply to 'coping with a living death' (Woods, 1989) in which 'the self' had long since vanished (Cohen and Eisdorfer, 1986). We next explore how person-centred care was central to the emergence of a new, more holistic vision of dementia and how responses could be formulated.

Person-centred care

As noted, during significant parts of the twentieth century, dementia had a chequered history with the provision of care being largely institutionally based and task orientated (Keady et al., 2009). Indeed, at the time, the meta-narrative of dementia was largely constructed around challenge, hopelessness, and the loss of self (for a review, see Nolan, 2003) with little, if any, effort made to provide supportive, evidence-based psychosocial interventions to enable people living with the condition to reach their optimum quality of life. This therapeutic nihilism was not to change until the introduction of reality orientation in the early 1980s (Holden and Woods, 1982) and the construction of a more sympathetic, and empathetic, policy architecture that began to value people with dementia. Two reports published one year apart proved particularly influential in challenging the prevailing public and professional attitudes at the time: *Organic Mental Impairment in the Elderly* (Royal College of Physicians, 1981) and *The Rising Tide* (Health Advisory Service, 1982). For the first time, these reports both signposted the importance and human worth of people with dementia and highlighted the need for well-staffed resources in both community and residential settings. In particular, *The Rising Tide* addressed the needs of both the person with dementia and their carers and set out the key components of a comprehensive service that was to include 'support, advice and relief at times of special difficulty to families' (p. 17) with primary health and social services seen as the 'essential ingredients' in providing a successful comprehensive service.

This commitment to improving the lives of people with dementia *and* carers was reinforced by the King's Fund Centre (1984) in a project paper that detailed the tenets of good service practice. This was achieved by

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outlining five 'key principles' that provided philosophical beliefs about personal empowerment for people with dementia. The five principles (King's Fund Centre, 1984; 7–8, slightly abridged) called for an acknowledgment that:

1. People with dementia have the same human value as anyone else irrespective of their degree of disability or dependence;
2. People with dementia have the same varied human needs as anyone else;
3. People with dementia have the same rights as other citizens;
4. Every person with dementia is an individual; and
5. People with dementia have the right to forms of support which do not exploit family and friends.

While this was a most helpful start, the case for putting the 'self' back into the individual experience of living with dementia was more eloquently articulated by Professor Tom Kitwood and his colleagues at the Bradford Dementia Group. They developed an elegant social theory of personhood in dementia that was, in time, to influence UK public policy and have a global impact. True to the philosophy of a person-centred approach, this model did not emerge from the consideration of data collected from significant numbers of individuals but, as with Alzheimer's work, was built around a single case history, or psychobiography as it was originally named, undertaken by Kitwood himself (Kitwood, 1990b). This psychobiography was conducted by Kitwood with a person called 'Rose', whose struggle to assert her personality through the mask of her confusion triggered Kitwood's thoughts on the need to reconceptualize the experience of dementia. After attempting to agree a meaning to Rose's actions and behaviours with colleagues at the Bradford Dementia Group (see Kitwood, 1990b for a fuller discussion), they constructed a multidimensional theory that identified a range of social and subjective factors that they believed shaped Rose's experiences. While the emerging theory focused predominantly on the more 'advanced' stages of dementia in residential care, mirroring Rose's personal circumstances, it nevertheless placed the person with dementia at its heart. It was from these observations that Kitwood (1988) reconceptualized the experience of living with dementia along the following lines:

$$SD = P + B + H + NI + SP$$

In this equation, SD refers to senile dementia, which is viewed as the product of the complex interactions between the remaining five elements of the equation:

P	Personality, which includes coping styles and defences against anxiety.
B	Biography, and responses to the vicissitudes of later life.

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H	Health statues, including the acuity of the senses.
NI	Neurological impairment, separated into its location, type, and intensity.
SP	Social psychology, which constitutes the fabric of everyday life.

Kitwood (1988) suggested that the equation accounted for most of the phenomena associated with the range of dementias and explained the unique course of each person's dementia by combining 'structural' and 'conjunctural' means of explanation. This theory reflects Kitwood's (1990a; 1997) critique of the past failings of care environments and approaches to people with dementia, which, for Kitwood (1990a), created a 'malignant social psychology' that inhibited the full expression and selfhood of people with dementia. Crucial to the emerging theory was the acceptance of the construct of 'personhood' and the recognition that a 'malignant social psychology' had been developed which 'bore down powerfully' on those with dementia (Kitwood and Bredin, 1992b). Kitwood (1990a) initially outlined ten components that illustrated the elements of this 'malignant social psychology' but later extended these to 17 by the time of the publication of the now-seminal text *Dementia Reconsidered: The Person Comes First* (Kitwood, 1997; 46-47). Examples of the factors that Kitwood believed created a 'malignant social psychology' include:

- Infantilization: implying that a dementia sufferer has the mentality or capability of a baby or young child.
- Stigmatization: turning a dementia sufferer into an alien, a diseased object, an outcast, especially through verbal labels.
- Outpacing: the delivery of information or instruction at a rate far beyond what can be processed.
- Objectification: treating a person like a lump of dead matter; to be measured, pushed around, drained, filled, and so on.
- Ignoring: carrying on (in conversation or action) in the presence of a person as if they were not there.

Kitwood and his colleagues cogently argued that 'the dementia' is not the main problem, rather it is 'our' (individual, carer, professional, society) inability to accommodate 'their' view of the world. Kitwood and Bredin (1992b) suggested that this 'them' and 'us' divide creates a dialectic tension that is reinforced over the years by the devalued status of someone who is labelled as 'demented' and who is consequently seen to be cognitively incompetent (see also Sabat et al., 2011). Underpinning these observations is the belief that if the elements of a 'malignant social psychology' can be identified, appraised, and overcome, then care (both for family and professional carers) can be improved and that the person with dementia will achieve a greater sense of personal 'wellbeing'. This

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focus on wellbeing is reflected in Kitwood's (1997) definition of personhood:

It is a standing or status that is bestowed upon one human being, by others, in the context of relationship and social being. It implies recognition, respect and trust. Both the according of personhood, and the failure to do so, have consequences that are empirically testable (p. 8).

To promote the practice of person-centred care, the observational method of Dementia Care Mapping (Kitwood, 1990a; Kitwood and Bredin, 1992a) was devised, with the goal not only of enhancing care in formal settings, but also of capturing it in a measurable way. Kitwood and Bredin (1992a) argued that a positive change to the social environment could cause a reversal of the accepted 'decline' trajectory in dementia (i.e. from mild to moderate to advanced stages) and named this 'reementia'. Such a paradigm shift had implications for the caring professions, as people with dementia were now seen to exert a sense of agency that could only be realized through significant changes in professional attitudes, practices, and cultures.

Following Professor Kitwood's untimely death at the end of the 1990s, the mantle of developing person-centred care was taken up by Professor Dawn Brooker who, at the time, was also working out of the Bradford Dementia Group in the UK. In a subsequent influential paper, Brooker (2004) developed the VIPS model of person-centred care:

- Value of all human lives;
- Individualized approach recognizing uniqueness;
- Seeing the world from the **P**erspective of the service user;
- Social environment that promotes wellbeing.

The VIPS model provides a helpful memory aide highlighting the importance and value of people with dementia as well as reflecting a more holistic appreciation of the relationships that infuse daily life. In a later text, Brooker and Latham (2015) extended the reach of the VIPS model to challenge the prevailing culture of care home attitudes and outlined the importance of 'getting person-centred care into everyday practice' (p. 24).

While Kitwood's work was promoting a new vision of the experience of dementia from the perspective of people who lived with the condition, a parallel stream of work was exploring the carer's perspective.

Dementia: Focusing on family carers

There is no doubt about the enormous impact that Kitwood's work has had on the care of people with dementia, with the previously largely nihilistic approach being replaced by a much more positive and dynamic model centred on the personhood of the individual. However, as noted,

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Kitwood's initial focus was largely on care provided in an institutional setting and, while the role of staff in creating a positive (or malignant) social psychology was acknowledged, the contribution of family carers was largely overlooked in the construction of person-centred care. This left a considerable gap in our understanding, for then, as now, the majority of people with dementia live in the community supported, as needed, primarily by family carers (Alzheimer's Society, 2014). Studies on the experiences of family carers for people with dementia have a long and distinguished history from early pioneering work conducted in the US by Zarit and colleagues (1980, 1986) and which continues to the present day. However, much of this early work was undertaken in North America and focused almost exclusively on the 'burden' of family care and the negative consequences that caring has on the health and wellbeing of family carers—a perspective that continues to dominate the landscape of dementia care and practice.

As Kitwood was developing his new approach to dementia care, a parallel but separate stream of work was being undertaken at Bangor University in North Wales that sought to provide a more rounded and holistic view of family care. The original focus of this work was on carers of older people and parent carers of people with learning disabilities rather than carers of people with dementia per se. It clearly demonstrated that a view of caring predicated on burden alone was inadequate and that, in reality, caring comprises a complex mix of burdens and rewards, and the balance between the two matters the most (Nolan and Grant, 1989; Nolan et al., 1990; Grant and Nolan, 1993). Several studies showed that carers' subjective interpretations of their situation and the nature and quality of their relationship with the person they were supporting were most influential in determining their levels of stress, rather than the objective circumstances of care, such as the amount of direct practical and instrumental help they provided (Grant et al., 1990; Nolan et al., 1990; Nolan et al., 1994).

This called attention to the dynamic nature of the relationship between carers and cared-for persons that was consistent with the [at the time] recently published and now seminal work of Kahana and Young (1990). These authors were ahead of their time in criticizing the largely unidirectional and unidimensional models of care that then predominated, in which the cared for person was seen only as a source of stress and burden on the carer, with universally negative consequences for the latter. Instead, Kahana and Young (1990) called for the development of more dynamic and relational models, which acknowledged and explored the possibilities of both negative and positive consequences for both the carer and the cared for person. Such 'dyadic' and dynamic models were, they argued, essential if more appropriate and sensitive support was to be developed. In looking to the future, these authors suggested that the dyadic model itself needed to expand to account for triadic interactions that included the perspectives of service providers as well.

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This work appeared as a book chapter (a source of expertise and inspiration that is sadly all too often overlooked today with the present hegemony of the 'journal'), coinciding with the work being undertaken at Bangor University, and stimulated further exploration into the relational dynamics of caring. In a seemingly serendipitous manner, at virtually the same time, American psychologist John Rolland (1988, 1994) published his model of working with people with disabilities, their family carers, and formal services, which he called the 'therapeutic quadrangle'. Rolland's interest was in the experience of living with and supporting people with long-term conditions, which he argued are far more heterogeneous in their presentation and effects than acute conditions. He postulated that, in order to develop truly responsive interventions, there was a need to look at the interactions between the person with a long-term condition, the family, and the professional system all within the context of living with a particular form of a chronic condition, which varies on several important dimensions, e.g. onset, course, incapacity, and outcome. Thus, he argued, a condition such as a stroke, which usually has a sudden and often unexpected onset, and causes varying degrees of incapacity but which subsequently follows a relatively stable course (in the absence of another episode), makes very different demands than a condition like dementia, with its usually insidious onset, highly variable and unpredictable course, and slowly increasing levels of incapacity. As such, it requires very differing forms of support for all concerned in the process.

The work of Kahana and Young (1990) and Rolland (1988, 1994), coinciding as it did with the newly emerging focus on the dynamics of caring relationship in the UK, exerted a considerable influence on the direction of future studies with Nolan and colleagues (1994) adopting the 'therapeutic quadrangle' as an organizing framework for much of their ongoing work (Fig. 15.1). Subsequently, Keady took the lead on a number of studies with people with dementia and their carers (Keady and Nolan 1994a,b; Nolan et al., 1995, 1996; Keady, 1996, 1997, 1999), and it is to this body of work that we now turn our attention.

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Fig. 15.1
The 'therapeutic quadrangle'.

Reproduced with permission from Nolan, M. R., Grant, G., Caldock, K. and Keady, J. (1994). *A Framework for Assessing the Needs of Family Carers: a Multi-disciplinary Guide*. Stoke on Trent: BASE Publications. p. 24.

Developing new understandings on 'caring' and the dementia experience.

Around the time that Rolland (1988, 1994) and Kahana and Young (1990) published their work, some exciting new insights emerged about the meaning of caring in dementia from the perspective of family carers. For example, Motenko (1989) highlighted the potential for carers of people with dementia to experience both gratifications and frustrations, thus reinforcing Hirschfield's (1981, 1983) earlier conclusions on the importance of mutuality in caring relationships, or the extent to which carers find gratification and meaning in their role. Concurrently, Barbara Bowers, an American nurse, was exploring the meanings that caregiving daughters of people with dementia give to their experiences and developed a much more sophisticated and nuanced typology of caring (Bowers, 1987). The next few sections describe briefly the types of care, many of which were deliberately kept 'invisible' from the person with dementia, and some of which occurred a long time before actual hands-on instrumental care was needed.

Anticipatory care

This typically occurs long before any physical care is needed and involves carers anticipating what they would do if ever care was needed in the future. However, while this is a cognitive and speculative activity it can still have a profound effect on people's lives, for example, in the case of an only daughter who may not move overseas in anticipation that her ageing mother might need care in the future.

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Preventive care

This typically comprises caring at a distance and involves subtle efforts to 'keep an eye' on an ageing parent, for example, to see that they are taking medication or that their diet remains good. This is more overt and purposeful than anticipatory care, but is still nevertheless largely hidden from the older person.

Supervisory care

This type of care is now becoming increasingly obvious and comprises more direct action, such as shopping with/for the older person, directly ensuring they take medications, checking to see that their fridge is adequately stocked, and taking action if it isn't.

Instrumental care

This is the type of activity most usually defined as caring and involves providing direct hands-on assistance usually with a range of activities of daily living or instrumental activities of daily living. It is the primary type of 'caring' activity that is recognized as such by formal services, and often the only type of care for which a carer is likely to be offered help.

Protective care

This again comprises a subtle range of activities which daughters [in the theoretical sample that predominantly comprised the study] undertook to 'protect' their mothers from knowledge of their increasing frailty and cognitive abilities.

Bowers' (1987) data indicated that it is protective care that daughters see as the most stressful and the most important, and instrumental care that they see as the least stressful and important. However, paradoxically, services focused almost exclusively on the latter and did not usually even acknowledge the former. This was often a source of conflict between family and paid carers.

While much taken with this model, at the time we argued that, based on our data collected over a number of years, anticipatory care was not confined to the early stages of caring (as Bowers contended) but occurred throughout the caring trajectory (Nolan et al., 1995, 1996). What changed was the nature of what was being anticipated. Moreover, we also suggested that while it was usually well-meaning, protective care could be potentially paternalistic and that the best caring relationships were characterized by *reciprocal care* in which both parties made a valued contribution. Another important element to the caring dynamic was *reconstructive care*, in which carers helped the person they were supporting to reconstruct a positive view of themselves. It was how such reconstructive and reciprocal care developed over time that was the primary focus of Keady's ongoing work.

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Building on a temporal model of the dementia caring experience as it unfolds over time (Wilson 1989a,b), Keady (Keady and Nolan 1994a,b; Nolan et al., 1996; Keady, 1996, 1997, 1999; Grant et al., 2003) developed a six-stage model of the caring trajectory that comprised the following phases:

- Building on the past
- Recognizing the need
- Taking it on
- Working through it
- Reaching the end
- A new beginning

'Building on the past' acknowledges that caring relationships do not appear fully formed 'out of the blue', but rather are usually preceded by a long relationship and that the quality of this relationship is very influential on the subsequent caring dynamic. 'Recognizing the need' is a period, either extended (as in dementia) or short (as in stroke), when the carer becomes aware that the nature of their relationship with their loved one is changing and that differences in roles and responsibilities are becoming apparent. 'Taking it on' should be a time when informed decisions about whether or not to 'become a carer' are made, based on as full an understanding of the potential consequences as possible. However, this rarely happens in practice and carers often 'take on' their role uninformed and lacking the skills and knowledge that they need to 'do caring well' (Schumacher et al., 1998). 'Working through it' is often described as the 'long haul' of caring and is the period during which, if they get any support at all, that carers are most likely to be in receipt of formal services. Sadly, they are rarely supported when they 'reach the end' either through the death of the person with dementia or their placement in a care home. At such times, carers often receive no support at all. Of course, for many carers, this is not the end of their support for the person with dementia, as the family will often continue to play an important part in the lives of the person with dementia. It is here where 'A new beginning' enters the life of (ex) family carers and different opportunities open up, which may, or may not, include continuity and exposure to dementia, e.g. taking on a voluntary role with the Alzheimer's Society or taking part in one of the many dementia café initiatives that are in existence across the UK. However, as far as services are concerned, their role as a 'carer' has ended.

Keady originally developed this model following in-depth interviews with carers of people with dementia (Keady and Nolan, 1994a,b; Keady, 1999) and it was subsequently elaborated upon with data from carers of physically frail older people and parent carers of people with learning disability (Nolan et al., 1996). While these studies tended to fit into the existing paradigm of treating people with dementia and carers separately, towards the end of his interviews Keady was able to involve some people with dementia. Consequently, a much more subtle picture began to emerge (Keady, 1999; Keady and Nolan, 2003), which allowed the

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'dynamics' of dementia to be better understood. Keady was able to describe a delicate and often longstanding dialectic that took place between the person with (as yet undiagnosed) dementia and their carer, in which the former began to notice that something was wrong and made efforts to hide this, and the latter sooner or later 'suspected' that something was wrong and made efforts to try and find out what (Keady and Nolan, 1995a,b; Keady and Gilliard, 1999). This involved 'boxing and coxing' in which both parties 'worked' hard but often towards different ends and sometimes to the detriment of their relationship. In such circumstances some carers and their partner tended to 'work apart' over time (Keady and Nolan, 2003). On the other hand, when couples developed an open stance to the changing behaviour of one partner and were more proactive in discussing potential difficulties and addressing them positively then they 'worked together' far more effectively. As the dementia was diagnosed and progressed over time, it was the carer who increasingly did most of the 'work' and Keady termed their efforts to keep the person with dementia engaged as 'maintaining involvement' (Keady, 1997).

Since that time, several studies have further explored the dynamics of caring relationships in dementia (e.g. Brodaty et al., 2003; Selwood et al., 2007) and our understanding moved closer to addressing Kahana and Young's (1990) prophetic call for the development of much more intricate models of the 'give and take' of caring relationships as they unfold over time. Recent studies have also seen the emergence of 'couplehood' in dementia, capturing, in more nuanced ways, dementia as a shared experience.

From personhood to couplehood

Probably the most extensive of these studies was that undertaken in Sweden (Hellström et al., 2005a,b; Hellström et al., 2007), which involved following 20 couples (where in each, one had dementia) over a five-year period and, wherever possible, interviewing both spouses several times. In total over 150 interviews were completed. This study has, to the best of our knowledge, collected the most extensive data of this type yet available and demonstrated several important points. Firstly, that it is possible to obtain rich and meaningful data from people with dementia over an extended period of time, with 12 of the original 20 people with dementia still being interviewed five years later. Secondly, for most of the spouses the idea of 'couplehood' was far more meaningful than was the idea of 'personhood' in that both parties described themselves primarily in relation to each other, rather than as separate individuals. Thirdly, in the majority of relationships, both spouses adopted a wide range of subtle tactics to ensure that they both experienced the best quality of life possible. Fourthly, until the very late stages, the person with dementia was a very active participant in 'maintaining involvement' and often developed deliberate strategies to 'hand over' responsibilities to their

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partner when they appreciated that their own capacity was becoming limited.

In describing these interactions Hellström et al. (2007) identified a wide range of processes, some of which reflected well-established patterns of relating, others of which had been developed and evolved in response to the dementia experience. Taken together, these processes created a 'nurturative relational context' (Hellström et al., 2005a,b) in which spouses sought to both 'sustain couplehood' and to 'maintain involvement'. In order to do so, they focused their attention primarily on the present, rather than looking too far into the future, but at the same time they often 'took risks' so that the person with dementia was not unduly constrained in their actions. However, most of their focus was on the dynamics of their relationship and involved:

- 'Talking things through', so that each partner was aware of the thoughts and feelings of the other;
- 'Being appreciative and affectionate', and complimenting each other on their appearance and the efforts they made to keep their relationship 'special';
- 'Making the best of things' by sharing enjoyable activities, seeing the positive things in life, and living for the moment; and
- 'Keeping the peace', which involved being aware of, and seeking to avoid, those activities that triggered a negative response in their partner.

As mentioned, this subtle range of activities were actively practised by both spouses, often over a prolonged period of time. Studies of this kind attest not only to the importance of relationships in understanding the dementia experience, but also to the continued agency of the person with dementia. These findings continue to hold resonance and meaning in the current literature (e.g. Wadham et al., 2016).

Although it had taken over a decade, studies such as these were now beginning to realize the vision of Kahana and Young (1990). The insights provided by such knowledge have implications for the care and support given to people with dementia and their family carers (which we consider shortly). However, before doing so, there is a need to describe an approach that more fully realizes Rolland's (1988, 1994) aspiration of a 'therapeutic quadrangle'.

Squaring the quadrangle: The Senses Framework and relationship-centred care

Following Kitwood's (1997) pioneering work, 'person-centred care' became a watch word for good quality individualized care for people with dementia and his ideas have been further developed by Brooker (2004) and Brooker and Latham (2015). However, the notion of person-centred care has also become the policy 'mantra' of the last decade and the

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'personalization' agenda still dominates policy pronouncements (e.g. Social Care Institute for Excellence, 2010). Unfortunately, unlike the contribution of Kitwood and, separately, Brooker, whose work has had an undoubted impact, the reality of policy rarely matches the rhetoric and there remains considerable confusion about what 'person-centred' care actually means (McCormack, 2004). Increasingly, at least in policy terms, it has become associated with concepts such as independence and autonomy, with a focus on the 'individual' and their circumstances rather than the nexus of relationships in which we all participate. This reflects the move towards the application of consumerist principles to health care (McCormack, 2004) and the emergence of concepts such as successful ageing, which lionize independence and autonomy (Scheidt et al., 1999). This represents a retrograde step, and overlooks the complexity of the vast majority of real-life situations, especially in conditions such as dementia. Ethicists like Evans (1999) and MacDonald (2002) have become increasingly critical of the 'politics of independence', arguing that such a stance tends to negate the shared responsibility that we all have to provide adequate support for the frailest and most vulnerable members of society.

The tensions apparent in many modern day health and welfare systems, with their goal of promoting independence, were acknowledged a number of years ago by a major 'task force' established in the US to consider creating a health care system fit for the future needs of American society (Tresolini and Pew-Fetzer Task Force, 1994). Following a period of 'intense national debate', it was recognized that the current system did not meet the needs of a population that was increasingly ethnically diverse and also lived primarily with long-term conditions. Such conditions pose the greatest future challenge to health care, but the system in the US, possibly even more so than in the UK, is not geared to address acute care needs. The task force concluded that there was a need to develop an entirely new model of health care, predicated of a different philosophy and they termed this 'relationship-centred care'. They determined that:

... relationships are critical to the care provided by nearly all practitioners and a sense of satisfaction and positive outcomes for patients and practitioners. Although relationships are a prerequisite to effective care and teaching, there has been little formal acknowledgement of their importance and few formal efforts to help students and practitioners learn to develop effective relationships in health care (Tresolini and Pew-Fetzer Task Force, 1994; p. 11).

In promoting a more holistic vision of health care the Task Force focused on several areas including the:

- Social, economic, environmental, cultural, and political contexts of care;

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- Subjective experience of illness; and
- Reality that relationships develop between practitioners, patients, families, and the wider community over time.

They suggested that it was the interaction of these factors that should lie at the heart of a health care system based on relationship-centred care and that relationships form the 'foundation' of any therapeutic or healing activity. While they went on to outline the basic elements of such a system, they also recognized that the concept of relationship-centred care was still emerging, and that further work was needed to put the concept into practice in ways that ensured an appropriate balance between the needs of everyone involved in health care relationships. The 'Senses Framework' (Nolan, 1997; Nolan et al., 2001, 2002a,b, 2006) provides one way of achieving this.

The 'Senses Framework' was developed in parallel to, but without awareness of, the emergence of relationship-centred care described here. Its roots lie in the early work of Nolan, Grant, and Keady (1996, 1998) on the caring relationship and the influences exerted by Kahana and Young (1990) and Rolland (1988, 1990) mentioned earlier. Mulrooney (1997) provided further stimulus at the World Congress of Gerontology in Adelaide, Australia, where he promoted a vision of person and relationship-centred care that was not based on notions of autonomy and individuality, but rather was predicated on three core principles:

1. Respecting personhood
2. Valuing interdependence
3. Investing in caregiving as a choice

This model, while recognizing that each person is unique and has individual needs and intrinsic worth, sees people as being primarily interdependent, a value base that recognizes the reciprocity that is inherent in the best of relationships and promotes a balance between dependence and independence (Mulrooney, 1997). However, in situations where substantial care and support are required, personhood can only be respected and interdependence valued if the person providing the care does so willingly. This may not always be the case for family carers. Such considerations also apply to those in paid caring roles, whether professional or not. Indeed, this belief was central to Kitwood's (1997) vision of person-centred care, and he argued that if paid carers are not valued and accorded status then they will bring a feeling of being devalued into their work, which will inevitably be reflected in the care they provide for people with dementia.

An invitation to deliver a keynote address on the future role of nurses in the delivery of health and social care for older people (Nolan, 1997) led to the emergence of the 'Senses Framework'. The paper focused in particular on addressing the needs of frail older people who require ongoing support. It argued that the evolution of modern-day health care had put 'cure' centre stage and that caring had become an essentially

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devalued activity. As a consequence, those working in acute care have a clear sense of therapeutic direction and an explicit goal, cure, to which they aspire. Moreover, such a goal is highly valued and the 'excitement' and 'value' of working in an acute, hi-tech environment is constantly reinforced in the media and exalted by the public. In the absence of cure, the fledgling discipline of geriatric medicine substituted rehabilitation, based on achieving a certain degree of functional independence, as its therapeutic aim (Wilkin and Hughes, 1986). However, those working in longer-term care environments have always lacked a sense of therapeutic direction, hence the nihilism described by Kitwood (1997). The efforts of those working in long-term care have been consistently denigrated and accorded little or no value and status, as reflected in the academic literature, where it has been termed 'aimless residual care' (Evers, 1981), or at best 'good geriatric care' (Reed and Bond, 1991) where the aim is to keep older people safely 'warehoused'.

Nolan (1997) argued that, given the prevailing demography with those aged 85+ being the most rapidly increasing section of the population, health and social care had to create a positive environment for long-term care in order to ensure that the needs of frail older people were adequately met and that those providing care could experience a feeling of job satisfaction. He suggested that in a positive long-term care environment, older people should experience six 'Senses':

- *Security*: feeling safe physically, psychologically, and existentially;
- *Belonging*: maintaining important relationships and feeling part of a valued group or community;
- *Continuity*: creating links between the past, the present, and the future, and experiencing consistent care delivered by known people;
- *Purpose*: engaging in valued activities and having something to ensure the meaningful passage of time;
- *Achievement*: achieving valued goals and feeling that all efforts are valued; and
- *Significance*: to feel that each individual, who they are, and what they do in some way 'matters' to others considered important to that person.

However, he also argued that if staff were to create such an environment for older people then they, too, have to experience the 'Senses' for themselves. So, for example, staff need to feel secure in their terms of employment and that it is safe to raise any concerns they might have about standards of care; that they belong, not only to a staff team or group, but also to a wider community of practitioners—something that is hard to achieve in many long-term care environments where staff turnover is often very high, which compromises the Senses of belonging and continuity. The lack of therapeutic direction in long-term care has already been alluded to, and this seriously erodes a Sense of purpose and achievement for staff. The low status of work with frail older people (and

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indeed those whose needs fall outside the acute sector generally such as people with learning disabilities) and the lack of importance accorded it means that there is little to be gained by way of a sense of significance. Small wonder then that standards of care have been historically poor, as captured graphically in the titles of seminal works such as *The Last Refuge* (Townsend, 1962) and *Sans Everything* (Robb, 1967). Despite considerable improvements, scandals still arise with uncomfortable regularity.

The success of Kitwood's work and the enthusiasm with which it has been adopted is probably due in no small measure to the fact that it helped to create the Senses for staff working with people with dementia. After years of therapeutic nihilism, they suddenly had a sense of purpose (to realize person-centred care) and, with the advent of dementia care mapping, a way of demonstrating that they had achieved this. As the popularity of this approach spread, it helped to create a sense of belonging for an increasingly large group of people delivering person-centred care, and as the value accorded to this grew, so too did the sense of significance and importance attached to this area of practice.

While initially the Senses were largely conceptual, lacked a clear empirical basis, and had been developed with a long-term setting in mind, a major study in 1999 (Davies et al., 1999) demonstrated their value in an acute hospital context. Following the publication of the *Not Because They Are Old* report (Health Advisory Service 2000, 1998), which once more highlighted the lamentable standards of care received by older people in acute care settings, Davies and colleagues were commissioned by Help the Aged and the Orders of St John Care Trust to identify acute hospitals in which older people and their families had received good care, and to explore what it was that differentiated them from settings in which older people received poor care. Following a number of detailed case studies, Davies and colleagues (1999) concluded that it was the leadership of the ward sister (manager) that was the primary factor. In care environments in which older people and their families praised care, the sister created a 'positive culture', which had at its heart three essential features:

1. 'Valuing fundamental practice', so that essential elements of care such as help with personal hygiene, feeding and toileting were given a high priority. Sister herself often took part in such activities and provided a clear role model. Such work was seen as 'significant' and provided a strong sense of purpose and achievement.
2. 'Fostering a stable environment', where there was little staff turnover, thus creating a strong sense of belonging and continuity. At the same time, staff felt safe to question practice and innovate where this was seen as necessary.
3. 'Establishing clear and equitable therapeutic goals', so that staff knew what was expected of them. This involved negotiating the goals of care with the active involvement of older people and their families.

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This study demonstrated the value of the Senses in an acute setting and identified a wide range of factors that created the Senses not only for staff and older patients but also for family carers (Davies et al., 1999).

During this and later studies, an environment in which the Senses were met for all the major stakeholders, and not just one group, e.g. older people or staff, was termed an 'enriched environment' (Nolan et al., 2002a, 2006; Brown et al., 2008) and this is captured in Table 15.1.

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Table 15.1 The components of an enriched environment.

Stakeholder Senses	Older person	Staff	Family carers	Students
<i>Security</i>				
<i>Belonging</i>				
<i>Continuity</i>				
<i>Purpose</i>				
<i>Achievement</i>				
<i>Significance</i>				

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The matrix also includes students as studies showed (Nolan et al., 2002a, 2006; Brown et al., 2008) that if students experience an enriched learning environment during their clinical placements, then they are far more likely to choose to go and work with older people than if they experience an impoverished environment, where the Senses are not created. Importantly, the 'Senses' have been developed, refined, and shaped with the active involvement of staff, older people, family carers, and students who have taken part in several studies spanning a number of years (Davies et al., 1999; Nolan et al., 2001, 2002a, 2006; Faulkner et al., 2006; Brown et al., 2008).

Recently, Nicola Hatton (2014, 2016) has taken forward some of the ideas of relationship-centred care and has argued that wider social, environmental, and cultural factors are also very important. Here, Hatton (2016) is developing ideas around the person with dementia's relationships with non-human artefacts, for example through: i) familiar sounds and smells of the care home and how a sense of belonging, for example, can start to be engendered through this sensory exposure; and ii) the use and access to familiar material possession(s) to help give the person a sense of security. This addition, then, opens the door for relationship-centred care to be coupled with embodied selfhood and affect.

Now that we have considered the evolution of relationship-centred care and the Senses, the next section presents a case study that describes an application in a care home setting and where one of the chapter authors (JK) was involved.

Relationship-centred care and the Senses Framework: A case study of the Senses in Practice (SiPs)

This case study is taken from a project that involved two care homes in the North West of England between June 2009 and September 2010 (Keady et al., 2011), though here we concentrate on just one of the homes. The overall aim of the Senses in Practice (SiPs) pilot training programme was to develop a staff education programme reflecting the importance of relationships and providing staff with an opportunity to identify how they might enhance the care of people with dementia using the Senses Framework. Nolan and colleagues (2008) suggest that educational interventions need to be embedded into an organizational culture that provides opportunities for staff to engage in problem solving and promotes relationship-centred care.

The objectives of the SiPs project were to:

- Develop and deliver a training programme that encouraged staff to develop dementia care practice using the principles of relationship-centred care and the Senses Framework to build upon commitment and confidence;

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- Evaluate the impact of the training programme on the experiences of staff, residents, and families within the home;
- Evaluate how relationship-centred care contributes to the provision of individualized care.

The care home described here was a for-profit development in a residential suburb of the North West of England. The care home had five 'houses' that allowed specialist care and attention, including to residents with dementia, with a total capacity of 150 residents. Four houses were registered for nursing care and one house was registered for dementia nursing care. The care home had single occupancy rooms and offered several different facilities on-site, such as hairdressing. The care home was awarded a Care Quality Commission rating of 2 (good) in the February 2010 inspection. Ethical approval to conduct the study was granted on 2 June 2009 (IRAS reference number 09/H1302/43).

Prior to the training programme, family carers were invited to share some of their thoughts about the care home and care provision, some of which are reproduced below:

- Staff always make me feel very welcome, chat to me during the visit. My husband seems much happier than he was in the last home he was in;
- It would be nice if there were more trips out;
- Recently the carpet and soft furnishings have been renewed. This has made the visiting much more pleasant.

The SiPs training programme

The SiPs training programme comprised eight sessions lasting one hour. The sessions were facilitated predominantly in a designated training room. The sessions were jointly delivered by JK (Professor of Older People's Mental Health Nursing) and CS (Research Associate with a PhD background in dementia care) and followed a similar cycle, with each session focusing on a different Sense and structured as shown in Table 15.2.

Table 15.2 Sessions of the SiPs training programme.

	Title	Activity
1	Knowing why we care: understanding the values and skills we bring to caring.	Completion of attitudes and values questionnaire.
2	Creating a sense of continuity.	The use of life story work.

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3	Creating a sense of significance in everyday practice.	The use of memory chests.
4	Creating a sense of belonging in everyday practice.	Understanding what home means to people.
5	Creating a sense of purpose in everyday practice.	Understanding how we each define purpose in our everyday lives.
6	Creating a sense of achievement in everyday practice.	Understanding what makes people happy in their lives.
7	Creating a sense of security in everyday practice.	Feeling safe with those around you.
8	Putting it all together.	Discussion of record keeping to reflect how staff implement the Senses Framework for people with dementia.

The training programme comprised a series of interactive workshops where staff were encouraged to consider how important each of the Senses was for them as individuals in their own lives using activities and guided discussions. Staff were encouraged to draw on their personal and professional experiences and were supported in further discussions focusing on how their knowledge and understanding might improve the experience of routine care for people with dementia. Each staff group developed their own definitions of the Senses Framework to support their use in practice (see Table 15.3). The timing of the sessions was carefully negotiated to ensure maximum staff attendance and minimum disruption to the home. Nonetheless, attendance at the workshops fluctuated, although there was always a 'core group' of attendees.

Table 15.3 The Senses Framework and meanings: An overview developed by care home staff.

Sense	For Residents	For Families	For Staff
<i>Purpose</i>	Sense of identity; Individual care.	Recognizing the family's importance of caring for the resident.	Having a goal; Being needed; Being recognized by residents.

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<i>Achievement</i>	Accomplishment; Being content.	Involving families in the care of the resident.	Developing a life story book with one of the residents; Creating memory boxes with residents and their families.
<i>Security</i>	Familiarity with the environment; Familiar voices; Having keys (such as door keys); Memories; Routines; Stories of 'home' or the place the resident grew up; Directions to bedroom; Photographs and belongings in the bedroom.	Having a key worker to talk to; Knowing the resident is 'safe in the hands of staff'; Having the opportunity to be involved with the activities; Getting to know the staff and who they are; For staff understanding the resident's biography; Staff recognition that not all families want to visit and there are many different reasons for this; 'Christmas families'.	Feeling wanted; Being recognized by residents and their families; Team working (especially between day and night staff); Being flexible; Knowing people; Working on the same unit and developing relationships ('smiling faces'); The joy of caring.
<i>Significance</i>	Being treated as an individual.	Involving families in helping to develop life story books	Accomplishments being acknowledged.

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		and memory boxes.	
<i>Belonging</i>	Feeling of community; Familiar things, such as photographs and ornaments.	Being included in the running of the home; Being comfortable; Feeling integral to the care home.	'Home' and what 'makes a home'; Being part of the care home culture; Knowing staff and residents; Being comfortable.
<i>Continuity</i>	Routine; Things to do; Developing memory boxes and life story books; Continuity in terms of transition between home in the community and care home; Ensuring the well-being of residents.	Being involved in the resident's care; Being kept up-to-date.	Working on one unit; Learning about residents' life stories.

Reproduced with permission from Nolan, M. R., Brown, J., Davies, S., Nolan, J. and Keady, J. (2006). *The Senses Framework: Improving Care for Older People Through a Relationship-Centred Approach*. Getting Research into Practice (GRiP) Report No 2, University of Sheffield page 125

Through this approach, staff attending the training sessions developed a *Creating the Senses for ...* booklet which could be completed by residents, families, and staff. The purpose of the booklet was to offer insight into the resident's life, such as hobbies and holidays enjoyed. The booklet would be located in the resident's room, giving the resident a sense of ownership and empowerment. Moreover, during the sessions, the value of sensory boxes and memory boxes were discussed, and staff showed a keen interest in pursuing these ideas. Posters were displayed around the care home inviting staff, family members, and visitors to donate sensory items, particularly those with a reminiscence theme. As one of the care home staff shared on the final evaluation form: *'I look at the person [now], not the illness.'* It is a fitting testimony to the power of the Senses and life story work and their potential to transform lives and attitudes. It

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also provides an insight into how care home staff can develop an individualized activities role that is drawn from the biography of the person with dementia to complement their role in providing physical care.

The above case study was a pilot, but other more intensive interventions have demonstrated the potential for the Senses Framework to significantly improve outcomes for people with dementia, family carers, and staff in care home facilities. For example, a three-year study by Davies and colleagues (2007) actively engaged staff and families in enriching the environment in a care home for people with dementia and resulted in highly significant changes, including:

- The introduction of an activities programme
- Establishing a relatives' support group
- Designing and producing a welcome booklet for new residents and relatives
- Significant fundraising activities to support the work of the home
- The re-instatement of uniforms for staff (at the request of staff and families)
- A regular education programme for staff
- The creation of a 'skills profile' for qualified staff
- The introduction of PAT dog 'Missie'
- The entire re-design of the garden project with the input of local university students
- Significant building modifications.

Adapted from Davies, S., Atkinson, L., Aveyard, B., Martin, U., McCaffery, S. and Powell, A. (2007). Changing the culture within care homes for older people. In Nolan, M. R., Hanson, E., Grant, G. and Keady, J. (Eds.) *User Participation in Health and Social Care Research: Voices, Values and Evaluation*. Maidenhead: Open University Press, pp. 50–68. Copyright (c) 2007 McGraw-Hill.

Similar longer-term projects using the Senses Framework in the community have resulted in the introduction of innovative respite care schemes that have transformed the experiences of people with dementia, families, and staff (Ryan et al., 2008) and in providing a practice lens to view the meaning of interactions for younger people with dementia (Davies-Quarrell et al., 2010). However, these interventions do not represent 'quick fix' solutions and have involved considerable efforts that have fundamentally changed the culture of dementia care, much as was Kitwood's (1997) original goal. We conclude this chapter by looking to the future and suggesting two additional areas where we believe there is a need for culture change and where the Senses may have a role to play. These are the diagnostic process and addressing the needs of people with dementia and their families at a societal level.

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Wider implications of the Senses

Improving the experience of diagnosis

There is much current interest in the importance and value of an early diagnosis of dementia. For example, the benefits of early diagnosis may include relief from stress due to a better understanding of symptoms, risk reduction, and maximizing decision-making autonomy (Alzheimer's Disease International, 2011; 27). The same report (page 7) also suggested that receiving a diagnosis of dementia should be considered a human right and recommended that 'every country should have a national dementia strategy', with each strategy promoting early diagnosis and intervention through awareness raising, training of the health and social care workforce, and health system strengthening.

In the UK, the topic of early diagnosis is at centre stage of policy. Key commitment 1 of the first Prime Minister's Challenge on Dementia (Department of Health, 2012) was aligned to 'better diagnosis' and increasing diagnosis rates through regular (cognitive) checks for people aged over 65. Such a commitment is currently integrated into commissioning frameworks with financial incentives to reach improvement targets (Department of Health, 2012), set at 75% by 2017 across every area of England (Alzheimer's Society, 2015; 12).

While it could be argued that the current push towards early diagnosis and intervention is both laudable and necessary, the limited numbers of older (and younger) adults actually coming forward for a memory assessment to consider the existence of a dementia remain a cause for concern. For example, only 20–50% of people with dementia living in high-income countries have a diagnosis, with that percentage falling significantly in middle- or low-income countries (Alzheimer's Disease International, 2011; 4). These findings stand in contrast to the 'Value of Knowing' telephone survey (N=2,678) that examined public perceptions and awareness of Alzheimer's disease for adults aged 18 and over in five countries [US, Germany, France, Spain, and Poland: <http://www.alzheimer-europe.org/Research/Value-of-Knowing>; accessed 29 January 2018] where one of the main findings was that more than eight in ten adults—from 85% in Poland to 95% in Spain—said that if they were exhibiting confusion and memory loss, they would go to a doctor to determine if the cause of the symptoms was Alzheimer's disease.

These contrasting findings frame an important question, namely why, despite apparently positive public attitudes towards a diagnosis and increased policy and service attention in this area, does the under-reporting and underdetection of dementia exist? In response, a number of practical, sociological, and organizational explanations have been put forward, including: poor attitudes of general practitioners and primary care towards making a diagnosis (National Institute for Health and Clinical Excellence/Social Care Institute for Excellence, 2006; Manthorpe et al., 2013); stigma surrounding dementia and its diagnosis (MacRae,

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1999; Alzheimer's Disease International, 2012; Abley et al., 2013); an overall lack of professional knowledge about dementia (Ahmad et al., 2010); a threatening diagnostic process that probes for loss and not abilities (Keady and Gilliard, 2002; Samsi et al., 2014; Campbell et al., 2016); and limited public health information about dementia and its initial onset and presentation, especially as it impacts upon the neighbourhood and informal social networks (Keady et al., 2012; Ward et al., 2017).

All of the above suggests that, in terms of the Senses, there often currently exists an 'impoverished environment' with respect to people's first contact with the 'professional system' and their subsequent experience of the diagnostic process. So, a key question becomes: How can we create an enriched environment for people who suspect they have dementia and their families? We need to begin to explore how we can create a Sense of security when people first present with their fears about their 'memory' so that their concerns are not dismissed as 'just old age'. We also need to address the stigma associated with 'dementia' and, to that end, hopefully the work of people with dementia (e.g. the Three Nations Dementia Working Group, or the European Working Group of People with Dementia) can start to make a real difference. The priorities of the Three Nations Dementia Working Group (2017) are to:

- Bring the lived experience as experts with our personal knowledge of dementia that people value whether in a professional or non-professional capacity. As such our aim is to become the 'go to' group within the three nations (of England, Northern Ireland, and Wales) for anyone seeking input from people with dementia.
- Continue to contribute to society, to give value, advice, and information where required and requested.
- Help each other through mutual support, friendship, and understanding.
- Help all those affected by dementia. We understand your situation.
- Help those who are trying to help us (e.g. policy makers, service providers, academics, researchers, and businesses).

Against such a backdrop where citizenship and the social activism of people with dementia needs to be (rightfully) accommodated, we need to make the diagnostic procedure less potentially alienating and fragmented so that Senses of belonging and continuity are established from the outset.

Enriching the neighbourhood environment

In our view, there is also much that could be done to 'enrich' the community and neighbourhood environment in which people with dementia and their families live (Keady et al., 2012, 2014; Ward et al., 2017). Current strategies have started to take account of the everyday lives of people with dementia that take place in public places and spaces, such as in streets, shops, and civic amenities, e.g. the local leisure centre,

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cinema, public library, and so on (Alzheimer's Society, 2013). We wish to stress the responsibility that society has (not just professional services or carers) to enrich the life world of people with dementia.

Over the last five years, the rise of dementia-friendly communities has grown into a world-wide movement, with Japan as trailblazer, with many of its dementia-friendly city initiatives and public education campaigns being held up as international models of good practice (Alzheimer's Disease International, 2015). While the notion of what may constitute a dementia-friendly community is open to interpretation (Lin, 2017), Crampton and colleagues (2012) have identified four key dimensions: people, places, networks, and resources, with people living with dementia positioned at the centre of each dimension.

Arguably, it is at this personal-public space interface that relationship-centred care, as expressed through the Senses Framework, can be further developed to include a new dimension for people with dementia and their families—one that we have named 'the Neighbourhood Space'. In charting new directions that would improve the quality of lives for people with dementia and their families, we need to consider how 'the Neighbourhood Space' can be enriched so that people with dementia feel safe to participate more fully and to 'maintain their involvement' (Keady, 1997, 1999) with their community. With subtle additions to the original 'reach' of the Senses Framework, 'the Neighbourhood Space' now adds a further dimension that includes the relationships experienced by people with dementia and their families when living their lives 'outside the front door'. The Neighbourhood Space complements existing relationships with the family carer and care staff. It also sets a challenge for local civic amenities and transport providers, for example, to take into account the cognitive disabilities of dementia, and how these can affect judgment, decision-making, and recall, so that at the very least people with dementia experience a Sense of security in their environment.

However, to truly enrich 'the Neighbourhood Space', we need to address wider questions, such as how the Senses of belonging and continuity for people with dementia and their families be sustained; how we can ensure that they have access to meaningful activities that provide a Sense of purpose and achievement; and perhaps most importantly of all, how we can ensure that people with dementia and their families have a Sense of significance and genuinely feel that they 'matter' to the society in which they live. There is, of course, a significant part that professional and paid carers can play in addressing such questions, but the role of society as a whole is even more important. Extending the notion of a relationship-centred approach to care beyond the 'therapeutic quadrangle' will enable debate to occur at a fundamental level. This debate needs to address the values that society believes should underpin support and help for those in need. And it is a future challenge for us all.

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Psychological treatments

Chapter: Psychological treatments

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Introduction

Thirty years ago, a review of psychological treatments in older people concluded ‘therapists of all stances have been slow to respond to the needs of the aged ... exploratory work is beginning, however ...’ (Cooper and Murphy, 1986). The authors noted, in the literature of the time, psychoanalytical approaches predominated while work in cognitive therapy was beginning. Since then, there have been many developments in response to the specific needs of an increasing older population, including tailoring of interventions to embrace cognitive and physical changes, delivery of therapies in age-appropriate settings, and therapies with caregivers of people with dementia. Working psychologically with older people offers specific therapeutic opportunities. For instance, review of life experiences can be a rich therapeutic resource and can help in understanding the older patient’s current difficulties (Thompson, 2011). Providing therapies that include opportunities for social interaction can confer benefits (Pitkala et al., 2011). Engaging the family

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members of an older person can help to elucidate the beliefs and behaviours of the family that might be influencing the illness and adherence to a treatment plan (Stahl et al., 2016). There is now an optimism for the outcome of psychological therapies with older people and a recognition that the new cohort of ageing baby boomers will ask for more access to psychological therapies.

Psychological treatment studies with older people address a range of outcomes. As well as clinical endpoints such as symptom severity or remission of depression, other relevant outcomes might include impact on activities of daily living and quality of life, caregiver wellbeing, rates of care home admission, rates of progression from sub-syndromal to case-level illness, or prescribing rates of potentially harmful antipsychotic medication in dementia.

Older patients and their clinicians, in considering psychological treatment, need to be aware of their wide range of potential benefits and applications; these are summarised in Box 16.1. The aims and methods of different therapies overlap. For example, in both cognitive behaviour therapy (CBT) and interpersonal therapy (IPT), an important step in treating a depressed dementia caregiver might be to establish a new social network and, although the goal is the same, the two therapies will employ different techniques to reach it. This chapter provides an overview of the range of efficacious psychological treatments for older people with consideration of indication, access, and adaptation. CBT and IPT are reviewed in depth in Chapter 17 and Chapter 18.

Box 16.1 Indications for psychological treatments with older adults

- Patient preference, as an alternative treatment to medication, e.g. in the treatment of an anxiety disorder;
- To augment the effect of psychotropic medication, e.g. in the treatment of a depressive disorder;
- Prevention of progression from subsyndromal depression to case-level depression;
- Prevention of recurrence of depression;
- As part of a collaborative care intervention in the treatment of depressive illness;
- To foster adherence to medication, e.g. in the treatment of bipolar disorder;
- To avoid the use of potentially harmful medication, e.g. in managing behavioural symptoms of dementia;
- To help distressed caregivers, e.g. treating a dementia caregiver experiencing depressive and anxiety symptoms.

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Box 16.2 lists some of the therapies currently used with older people. Treatments can be divided into those devised specifically for older adults (usually to help patients with dementia) and those also used with younger adults (such as treatments for depression). Therapies in the first category include reminiscence therapy, validation therapy, and reality orientation. These were some of the first treatment approaches to be formalized and evaluated, starting in the 1960s. Reminiscence therapy uses group discussions, photographs, recordings, and objects to trigger personal memories and promote wellbeing. Many of the early trials used in their evaluation have significant shortcomings by today's methodological standards. A more recent large multicentre study of reminiscence groups for people with dementia and their family caregivers did not provide support for the efficacy or cost-effectiveness of reminiscence groups (Woods, Orrell, et al., 2016).

Box 16.2 Some of the psychological treatments used with older adults

- Cognitive behaviour therapy
- Problem-solving therapy
- Interpersonal therapy
- Systemic therapy
- Psychoanalytic and psychodynamic psychotherapy
- Reminiscence therapy
- Cognitive stimulation therapy
- Cognitive training
- Cognitive rehabilitation

There is now an increasing distinction between interventions that are of high intensity and low intensity. High-intensity interventions include CBT or IPT delivered by a therapist face to face (National Institute of Health and Care Excellence, 2017). In these, the therapist has flexibility in treatment delivery according to a formulation of each individual's problems. In contrast, low-intensity therapies are usually briefer, based on generic protocols for specific disorders, and typically involve guided written or audio-recorded self-help materials or Internet-delivered strategies supported by a therapist. The recent expansion of low-intensity interventions reflects a move to increase the availability of psychological treatments while limiting the costs of training therapists. In the UK, the Improving Access to Psychological Therapies (IAPT) programme was established ten years ago to provide high- and low-intensity interventions for depression and anxiety (Department of Health, 2013; www.england.nhs.uk/mental-health/adults/iapt/). Interventions may also be incorporated into stepped care programmes, whereby more intensive

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interventions are reserved for people not responding to low-intensity steps (van't Veer-Tzelaar et al., 2009). When able to access treatment via IAPT, older people tend to make good recoveries with low levels of attrition from treatment (Chaplin et al., 2015).

Making psychological treatments available to older people

Pettit and colleagues (2017) found referral rates of older adults to an IAPT service to be lower than those of younger adults. The proportion of those attending first treatment and showing clinical improvement increased with age. Several barriers to referral were suggested, including older patients' own perceptions of psychological treatments and communication problems between patients and doctors. Box 16.3 shows suggested methods for overcoming these barriers. Means of improving patients' access to treatment also include cognitive bibliotherapy (DiNapoli and Scogin, 2014) and Internet-based systems which appear to be acceptable to patients (Choi et al., 2014). However, the benefits of Internet delivery with or without support by a therapist are unclear (Olthuis, 2016). Delivery of therapy by telephone may overcome obstacles to access and stigma, although it is preferable to start with face-to-face sessions to establish a therapeutic rapport (Blanco et al., 2012). Therapy by telephone can pose additional challenges, e.g. being unable to observe non-verbal communications, and a greater susceptibility to distraction. Older patients favour an active rather than reflective participation in psychological treatment, an acknowledgment of spirituality, and discussion of their shame in seeking help (Dakin and Arean, 2012).

Box 16.3 Steps to increase the uptake of psychological treatment services by older people

- Increase the range of referral routes, such as via social services
- Offer a choice of venue
- Use age-appropriate advertising of services, such as posters in community centres
- Ensure that therapists understand lifespan development and needs of older people
- Provide interventions that give regard to long-term medical conditions

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A significant development in recent years is the use of collaborative care interventions with older adults. These multicomponent interventions include, for example, programmes to treat major depression and dysthymia (Hunkeler et al., 2006) or to prevent progression from

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subsyndromal to case-level depression (Gilbody et al., 2017). A key feature of a collaborative care intervention is the involvement of a case manager who delivers an intervention, e.g. problem-solving therapy or behavioural activation, while monitoring the patient's symptoms and providing a bridge between primary and secondary care services.

Taking account of sensory and cognitive changes

Deficits in verbal reasoning, speed of responses, and sensory function may result in difficulty understanding the complex verbal content of some psychological treatments. Therefore, evaluation for psychological treatment should include at least a brief assessment to look for possible deficits (Gallagher-Thompson and Thompson, 2010). Frequently asking patients to summarize their understanding of therapy sessions also helps the therapist to check a patient's understanding of therapy. Use of cued recall and recognition memory ('say it, show it, do it') also help to compensate for any deficits in spontaneous recall. Sensory deficits can often be circumvented by using technical aids or by audio recording therapy manuals for visually impaired patients. It is possible that psychotherapeutic strategies directly targeting deficits in planning and organizational skills may help to enhance response to antidepressant treatment (Pimontel et al., 2016). Adaptations of CBT and IPT are discussed in Chapter 17 and Chapter 18.

Psychological interventions in dementia

Psychotropic medications are known to be of limited benefit in treating depression and anxiety in dementia (Orgeta et al., 2017), so there is a need to develop and evaluate psychological approaches. The evidence for psychological interventions in dementia care has generally been derived from short-term studies, leaving a need for larger trials whose findings are applicable to real-world clinical settings and populations, including caregivers (Department of Health, 2011). There is also a lack of evidence of benefit on important outcomes such as quality of life and activities of daily living and a paucity of data on long-term efficacy and cost-effectiveness of psychological treatments in dementia (Orgeta et al., 2015). Cognitive behavioural and interpersonal therapy interventions for depression and anxiety in people with dementia and for caregivers are reviewed in Chapter 17 and Chapter 18 and interventions for people with dementia living in care homes are reviewed in Chapter 19.

Box 16.4 summarizes psychological treatment approaches to improve cognitive symptoms of dementia. Group cognitive stimulation therapy (CST) appears to boost cognitive function in people with mild to moderate dementia, although the duration of any benefits is unclear (Woods, Aguirre, et al., 2012). A model of CST adapted to improve access by enabling delivery by a caregiver or friend has been evaluated in a large study in the UK National Health Service (Orrell et al., 2017): no benefit

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was demonstrated in terms of cognition, quality of life, or caregiver wellbeing.

Box 16.4 Psychological treatment approaches to enhancing cognitive function

- *Cognitive stimulation*: Engagement in a range of group activities and discussions to enhance cognitive and social functioning.
- *Cognitive training*: Guided practice with individuals or groups on tasks to enhance particular cognitive functions using pencil and paper or computerized exercises.
- *Cognitive rehabilitation*: Individual therapy to address personally relevant goals with an emphasis on improving performance in everyday life, rather than on cognitive tests.

Source: data from Clare L., Woods RT. Cognitive training and cognitive rehabilitation for people with early-stage Alzheimer's disease: a review. *Neuropsychological Rehabilitation*, 14: 385–401. 2004, Taylor & Francis.

Systemic therapy approaches can lend useful perspectives in working with families coping with dementia. In systemic approaches, the family's beliefs and behaviour are understood as connected in a circular, rather than a linear, relationship (Anderson and Ekdawi, 2010). For instance, when a caregiver is known to be critical of a person with dementia who has become depressed, the criticism is not seen as the direct cause of the depression but as part of a dynamic interaction between both people's behaviours and emotions. This is illustrated in Fig. 16.1 and Fig. 16.2 in the case of Tom, a man with dementia, his wife Bertha, and their daughter. This perspective can help to facilitate communication when different views are held within a family; furthermore, it is useful when clinical staff have raised concerns about difficulties between family members. Principles of systemic therapy can be employed in routine meetings with patients and families by giving consideration to seating arrangements to facilitate connections, framing of questions to help generate goals, and by talking separately to different members in the family group in order to encourage reflection (Anderson and Johnson, 2010).

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Fig. 16.1

Linear causal explanation of the mood and behaviour of Tom, a man with dementia.

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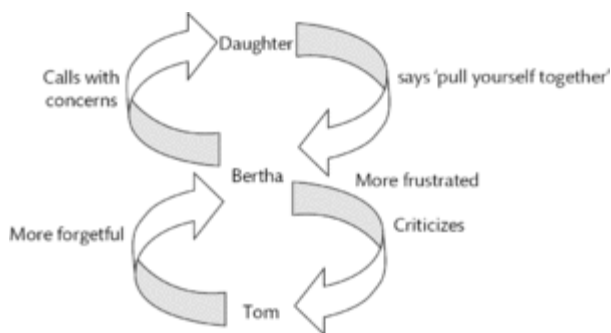


Fig. 16.2

Circular causal explanation of Tom's mood and behaviour.

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Cognitive behavioural therapy

Chapter: Cognitive behavioural therapy

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Introduction

Cognitive behavioural therapy (CBT) for older people is a mainstream treatment option for common mental health problems, e.g. depression and the anxiety disorders. CBT is particularly applicable as an intervention with older people as it is a problem-focused, skill-enhancing, individually empowering, present-oriented, straightforward-to-use method.

Over our professional careers, we have seen some important myths and misconceptions disproven about CBT with older people. The former consensus was that older people would not be amenable to modifying their thinking (cognitive restructuring) sufficiently for treatment to be effective; this clearly is not the case (Gould et al. 2012a,b; Wilson et al., 2008). Rather than being a natural outcome of the challenges associated with ageing, depression appears to be less common in older people and especially so when compared to working age adults, and Blanchflower

Cognitive behavioural therapy

and Oswald (2008) indicated that ‘Happiness is approximately U-shaped throughout the life-course; mental distress tends to reach a maximum in middle age’. Additionally, practitioners thought that older people would not want ‘talking cures’; on the contrary. For example, in primary care settings in particular, older people view psychological therapy as effective and as acceptable as medication but with fewer unwanted side-effects and, if given a choice, prefer to receive psychotherapeutic treatments rather than psychotropic medications (Gum et al., 2006; MacKenzie et al., 2008). As cohorts of older people change, we expect to see the use of CBT increase.

Another misconception was that older people are ‘too set in their ways’ to change. Data from longitudinal studies from gerontology (the science of ageing) testifies that emotional change occurs across our entire lifespan, and as one ages emotional regulation improves along with the experience of better emotional stability (Carstensen et al., 2011). One could argue that older people make better candidates for CBT because of having both positive and negative experiences across the lifespan; as a consequence, they may be more understanding of their own, and others’, frailties and of their own personal resources. Indeed, recent data from the National Health Service in England—where older people can access Improving Access to Psychological Therapies (IAPT) services—suggest older people achieve good treatment outcomes in comparison to working age adults (Chaplin et al., 2015). Based on national clinical data, on average, older people are recorded as having recovery rates of 64.3% compared to 50.1% for working age adults after a course of treatment (NHS Digital, 2017).

Cognitive behaviour therapy (CBT)

CBT was originally developed by A.T. Beck in the 1970s and subsequently applied successfully with older people by Thompson and colleagues in the 1980s (Gallagher-Thompson and Thompson, 2010). CBT has an elegantly simple model: the way one thinks about a problem has an impact upon one’s feelings and behaviours. CBT considers physical and psychological states to be two sides of the same coin and thus each affects the other (Laidlaw, 2015). When one is physically low one often feels psychologically low: think of a time when you have a very bad head cold, and you may understand. This simple model is very commonly known as the four components model of CBT (Fig. 17.1). In this example, Mr Adams, who has Parkinson’s disease, thinks people are looking at him and when he attempts to put air in his car tyres at the local garage this sets off a negative reaction. As can be observed, a negative vicious cycle ensues, with his negative thoughts generating negative effects and a subsequent deleterious impact on behaviour. At the same time, physical changes, e.g. increased heart rate and other negative sensations, convince him that he is inadequate to the task. CBT therapists use the model to identify cognitions and behaviours to focus upon in treatment.

Cognitive behavioural therapy

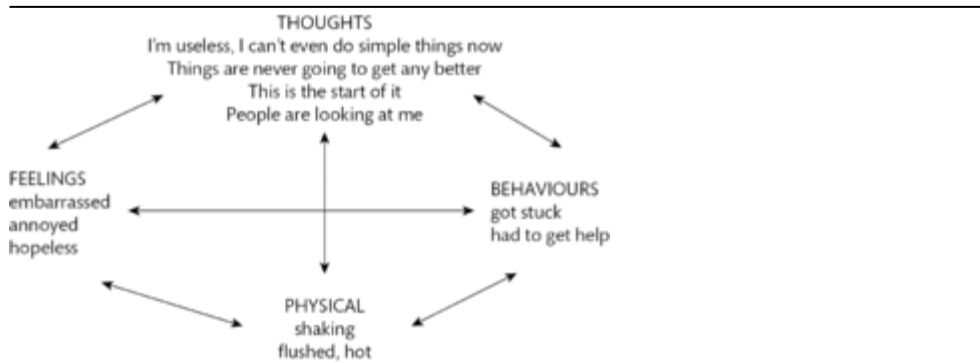


Fig. 17.1
Four components model of CBT.

Fig. 17.1 helps the patient understand the reciprocal nature of connections between thoughts, feelings, behaviour, and the physical state. Therapists alert their patients to the fact they can change the way they think about things and the way they behave. If thoughts and behaviours are connected to feelings and to physical consequences, then changing one element in this cycle can lead to change in everything. This model is used to socialize patients into the particular approach to symptom change adopted within CBT.

The model reminds us of another integral part of the CBT model, which states that it is not the *situation* that is problematic, per se, but how one *views* the situation that causes problems. This idea is not a new one—the stoic Epictetus said that ‘Men are disturbed not by things, but by the views which they take of them’. So, for Mr Adams, it is his thoughts that cause the problem, rather than the act of checking his tyres.

The central concept of the cognitive behavioural model is that emotional states, both positive and negative, are determined by the way in which the person processes information about the self and the world around. Negative automatic thoughts fuel unpleasant emotional states and particular patterns of behaviour which, in turn, maintain distorted thinking patterns (Beck et al., 1979). Unhelpful negative thinking patterns may be triggered by events in the outside world, but underlying these are belief systems, or assumptions, that are often quite specific to the individual. Older people may hold personal beliefs that were helpful to them in their younger years, but that give rise to problems in the face of negative life events or impoverished social circumstances in later life (James, 2010). For instance, an older woman who holds the belief ‘my place is in the family’ may lead a contented life for many years, only to become depressed when her adult children and grandchildren move away from her area, leaving her on her own.

In CBT, information about the patient’s thought patterns and underlying beliefs are used to derive a case formulation. A formulation can be thought of as a jigsaw puzzle that brings together pieces of information in

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order to see the full picture. Formulations describe how an individual experiences the world and responds habitually to challenges and difficulties. They incorporate the information about a patient that is important for understanding how the person is affected by their current difficulties and what may be important idiosyncratic appraisals the individual is prone to making. Formulation in CBT recognizes that there are overt elements (thoughts, feelings, behaviour) and covert elements (core beliefs and conditional beliefs, also known as maladaptive belief structures, or schemata). Developing a formulation with a patient is helpful at the early stages of therapy in order to predict difficulties and identify potential obstacles to a good outcome. Fig. 17.2 shows a depression formulation schematic based on the Beck model of CBT, which is the most commonly used CBT format.

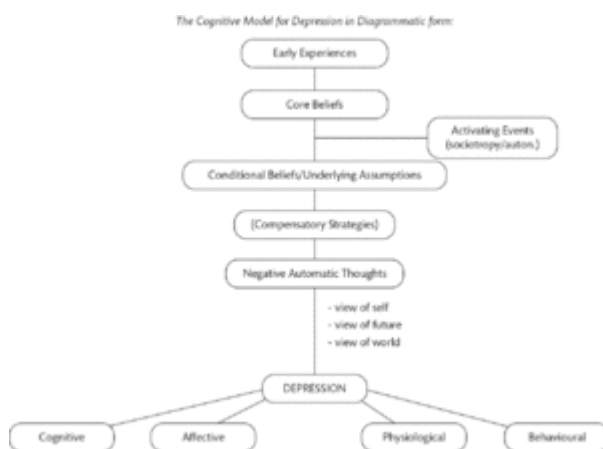


Fig. 17.2

Beck model of CBT and formulation diagram for depression.

A formulation in CBT helps the therapist and patient to reach a shared understanding of why and how an episode of depression or anxiety has come about, devise therapeutic interventions, and keep the therapy on track. This formulation-driven approach to treatment is combined with an empirically based treatment protocol specific to the disorder in question. Formulations can take many forms, according to the needs of the patient and the aims of the intervention (James, 2010). CBT is usually delivered to the patient as an individual; when it is used as a group treatment, there is a greater emphasis on the disorder-specific formulation than on individual formulations.

When working with older people there may be a need to take account of age-related factors. Laidlaw and colleagues have produced a comprehensive conceptualization framework (CCF; see Laidlaw et al., 2004) to help therapists apply CBT with older people by providing a way of framing or contextualizing problems within the standard CBT model. The main elements of the CCF (Fig. 17.3) are cohort beliefs, transition in role-investments, intergenerational linkages, the sociocultural context,

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and health status. Each element serves to broaden the understanding that a therapist will draw on when working with older people. The therapist may find that some elements are more important than others when contextualizing the nature of the client's difficulties.



Fig. 17.3
Comprehensive conceptualization framework for CBT with older people.

The CCF emphasizes the importance of considering cohort values when working with older people. This is the idea that beliefs held by older people may be influenced by society and the generation into which they were born. In many cases, a patient will be four to five decades older than their therapist, and as such there will be differences in values, cultures, and understandings. Typically, these beliefs begin in childhood and are reinforced over the years. For example, there could be an important interaction between generational beliefs held by a cohort born during the 1930s in the UK, e.g. 'stand on your own two feet' (meaning it is wrong to ask for help), and cohort familial beliefs transmitted as family rules, e.g. 'never wash your dirty linen in public' (meaning remain circumspect about discussing emotional difficulties), or 'older people must not be a burden on their families', as well as ideas about illness such as 'depression is shameful'. These beliefs may become apparent in the early sessions of CBT if the patient seems reluctant to engage in treatment.

CBT involves an active exchange of ideas between patient and therapist, with the therapist able to draw upon a range of cognitive and behavioural techniques to help the patient to identify maladaptive thoughts and beliefs in order to modify unhelpful behavioural and emotional responses to situations. Negative thoughts may be tackled directly through diary monitoring or through the use of behavioural experiments. These are planned activities undertaken by patients in order to disconfirm existing unhelpful thoughts and provide evidence for new, more adaptive thoughts. Many of these exercises, or *homework*, are carried out between therapy sessions by the patient and backed up with written notes and records.

The competent delivery of CBT requires the therapist to work collaboratively with the patient. Treatment is supported by therapist

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supervision and use of therapist competence measures (Roth and Pilling, 2007). Measurement scales are used to assess the severity of the patient's symptoms as well as changes specific to CBT, such as the patient's thinking style and core beliefs. In the last decade a number of anxiety measures specifically for use with older people have been developed (Yochim et al., 2011). The Royal College of Psychiatrists' Faculty of Old Age Psychiatry (RCPsych, 2012) produced a useful assessment guideline for individual patient outcome measurement.

CBT in the treatment of depression with older people

A large body of evidence now supports the efficacy of CBT as a treatment for depression with adults of working age (NICE, 2018). Individual CBT is as efficacious as antidepressants in reducing symptoms of depression in people with mild to moderate depression and produces more enduring benefit than antidepressant treatment alone. CBT also appears to be better tolerated than antidepressants. Adding CBT to antidepressant treatment can also improve outcome in more severe depression and possibly in chronic depression and is well tolerated by older people (Hanson and Scogin, 2008).

There are a number of published clinical trials of CBT for late life depression. Most of these, however, have methodological shortcomings, e.g. small sample sizes, reliance on relatively young media-recruited participants, absence of suitable control groups, absence of robust intention-to-treat designs, and unspecified treatment protocols (Gould et al., 2012b). Comparison groups in these trials include other psychotherapies in individual and group format, placebo, waiting list, and antidepressant medication. Evidence reviews for the updated NICE Depression Guideline (2018) found data from five randomized controlled trials (RCTs) showing a positive effect of CBT in treating depression in people aged 60 and over compared with waiting list or treatment as usual, and data from two studies providing evidence of benefit in inducing remission. The benefits in older adults appeared stronger than in adults under 60, but these differences did not achieve statistical significance. Statistically significant data indicated that older people are less likely to drop out of treatment with CBT than younger adults. The authors of one of the studies included in the NICE review (Serfaty et al., 2009) conclude their results discredit the myth that depressed older people are simply lonely and only lack a listening ear to recover, as those in their talking control group did less well than those in the CBT treatment group. Group CBT has also been evaluated in the prevention of depression recurrence (Wilkinson et al., 2009), but currently there is insufficient evidence from which to draw any clear conclusion on its efficacy with older people (NICE, 2018). There remains a need for large, high-quality RCTs of CBT to assess the effectiveness and cost-effectiveness of CBT, including in combination with antidepressant medication, in people aged 75 and over.

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Content of CBT in the treatment of depression

CBT is a uniquely constructed format of psychological therapy with each CBT session sharing identical structural elements. The format of a typical CBT session includes agenda setting (identifying the focus of the session), a bridge between sessions (ensuring continuity of focus), symptom monitoring, review of previous homework tasks completed outside of the session, a focus on current problems, and agreement to work collaboratively. Behavioural strategies are used early on in treatment with the aim of making some immediate positive impact on mood and helping the patient to engage with therapy. Activity monitoring using a simple diary can show patients how inactivity worsens low mood and the effect of negative thinking on underestimating achievement and enjoyment. A typical course of individual CBT for depression lasts up to 16 sessions and involves cognitive and behavioural elements. Treatment is usually divided into early, middle, and late stages. The aims of the early stage of CBT treatment are to both establish a sound therapeutic alliance as well as a shared understanding of problems so these may be translated into goals for treatment. At the end of this stage it is usual to have shared a formulation with the patient. In the middle stage of CBT, there is an emphasis upon cognitive and behavioural change. During this stage of treatment there is a great focus on identifying and challenging maladaptive negative thoughts (termed cognitive restructuring). The primary aim of CBT is symptom reduction and this stage equips the patients with the skills to bring about such change.

Cognitive restructuring is usually achieved through the use of specific thought diaries completed by the patient as a homework task. Fig. 17.4 shows a clinical example. Mr. Gordon is recently retired and decides he wants to enrol in a short course. He is worried that at his age this would be beyond his capabilities. The therapist helps Mr. Gordon find ways to 'answer' negative thoughts using the diary with the assumption this skill will generalize into everyday use. In challenging negative thoughts (cognitions), patients are taught certain skills to use, e.g. looking for evidence for and against their thoughts. Additionally, the patient can ask himself what is an alternative way to think about this situation. The basis of cognitive restructuring is that there is always more than one way to think about a situation or an experience.

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1. What actual event or thoughts, or decisions or reactions led to the unpleasant emotion?	1. What thought(s) and/or image(s) went through your mind?	1. What emotion(s) (distress/anger/etc) did you feel at the time?	1. Use questions at bottom to compare a response to the automatic thought(s).	1. How much do you now believe each automatic thought?
2. What (if any) decreasing physical sensations did you have?	2. How much did you believe each one at the time?	2. How intense (0-100%) was the emotion?	2. How much do you believe each response?	2. What emotion(s) do you feel now? How intense (0-100%) is the emotion?
3. What (if any) increasing physical sensations did you have?	3. What (if any) increasing physical sensations did you have?	3. What (if any) increasing physical sensations did you have?	3. What (if any) increasing physical sensations did you have?	3. What will you do for the first time?
Talking on the telephone about starting an OCU (openings course)	When I'm not capable of doing it	Anxiety Frustration 90%	I've done a lot of courses over my lifetime and managed most of them. I have successfully completed 90% of all courses in my life. By focusing on how well I do I am focusing on a positive aspect of what I am aiming for. I won't know if I don't try	Worried but calm Anxiety 50% I will start the course

Fig. 17.4

Dysfunctional thought record in CBT: example of Mr Gordon.

The final stage of therapy encompasses two main tasks to accomplish; (1) the agreement of an appropriate termination point for therapy, and (2) the elaboration of a relapse prevention plan. In this stage the therapist is empowering the patient to become their own therapist outside of treatment.

Behavioural activation (BA)

Behavioural activation (BA) can be used as a component of CBT or as a stand-alone intervention in depression. It aims to overcome the lack of response-contingent positive reinforcement in depressed patients' lives. Negative life events are seen as decreasing the likelihood of adaptive behaviours for vulnerable individuals, which leads to a downward spiral of low mood and a decrease in motivation (Martell et al., 2010). The key strategy in BA is that frequency and occurrence of pleasant events are increased. Graded exposure and graded hierarchies are necessary tools to help a client get started on activities and problem solving is also necessary in order to overcome practical obstacles that may prevent the client from engaging in tasks. Depressed individuals are more likely to be sensitive to negative stimuli, and BA aims to increase the likelihood that beneficial patterns of behaviour will be positively reinforced. Small studies of BA with older people suggest benefit in reducing depressive symptoms, but further better-quality trials are needed (Orgeta et al., 2017).

Problem-solving therapy (PST)

Problem-solving therapy (PST) is a brief, active, goal-oriented intervention related to CBT. It can be used as a stand-alone treatment or its methods can be incorporated into a course of CBT. It offers a practical approach to overcoming the inactivity and impaired problem solving and decision-making that occur in depression. Patients are supported in generating and testing out a range of possible solutions to the difficulties they are encountering. For older people experiencing long-term illness, these solutions will take the form of practical adaptations to foster adaptation to disability. PST appears to reduce depression severity in

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older people, but more studies are needed to assess its effects on mood and disability (Kirkham et al., 2016).

CBT for late life anxiety disorders

The UK National Institute for Health and Clinical Excellence (NICE) concluded that CBT is an efficacious treatment for generalized anxiety disorder and panic disorder in younger adults (NICE, 2012). Research into treatments for anxiety disorders in older people, however, lags behind that in younger adults, and NICE, while recommending CBT to treat anxiety disorders in adults of all ages, makes no recommendations specific to older people. Most trials with older people have been published in the US and there are methodological issues as many studies enrol people in their 60s and 70s, rather than older people who may be routinely seen in clinical practice (Gould et al., 2012a). Stanley and colleagues (2009), in an RCT treatment for generalized anxiety disorder (GAD), has answered many of these criticisms with a study conducted in primary care settings showing good treatment outcome. Wuthrich and Rapee (2013) and Wuthrich and colleagues (2016) demonstrated that CBT is efficacious for comorbid anxiety disorder and depression—research especially welcome as it provides important outcome data for CBT with older people that is closer to the experience of treatment in routine clinical settings. Finally, Kishita and Laidlaw (2017) published the first meta-analysis comparing CBT outcome for GAD between older people and working age adults. This study confirms that CBT with older people is as efficacious for GAD as with adults of working age.

Content of CBT in the treatment of anxiety

While there is overlap between anxiety and depression in terms of symptoms and cognitions (negative predictions and a negative bias in appraising current experiences), in anxiety the negative appraisals tend to be more selective and specific to certain situations (Beck et al., 1985; Worlitzky-Taylor et al., 2010). The experience of anxiety may also tend to increase the probability of the feared event occurring. For example, a socially anxious patient may hesitate in social situations, thereby undermining social performance. There are a number of disorder-specific models of anxiety disorders. For instance, according to the cognitive model of panic disorder, sufferers misinterpret physical sensations of anxiety as signs of imminent physical catastrophe (Clark, 1986). In health anxiety, patients are afraid of having an undiagnosed serious illness; they monitor and overinterpret physical symptoms and engage in safety-seeking behaviours that exacerbate their anxiety (Silver et al., 2004). Patients with GAD experience a number of fears about their everyday circumstances and engage in repetitive worry in an attempt to solve problems. CBT for GAD focuses less on the content of worrisome thoughts and more on changing the process of managing worries.

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CBT in the treatment of patients with physical illness

In a classic text, Rybarczyk and colleagues (1992) outline five elements that therapists need to take into account when working with physical illnesses in depression and anxiety disorders: (1) practical barriers to participation in therapy; (2) accepting depression as a separate but reversible problem distinct from their ongoing physical problems; (3) identifying and limiting excess disability; (4) recognizing and limiting losses of roles and autonomy; and (5) challenging perception of oneself as a burden to others. CBT can be a good fit for older people living with long-term physical conditions as it encourages self-efficacy in the management of their condition and often provides a problem-solving approach to the challenges of living with a long-term condition. CBT has been shown to be efficacious for depression in a number of physical conditions. For example, Dobkin and colleagues (2011) evaluated CBT for depression in Parkinson's disease. The CBT group reported significantly greater reductions in Hamilton depression (HAM-D) scores, and significantly more treatment responders at the end of treatment (56% versus 8%) in comparison to the group who received clinical monitoring only. Evidence for the efficacy of CBT for post-stroke depression is currently limited to two small trials (Kneebone and Jeffries, 2013; Thomas et al., 2013) and more research is necessary. A recent review of the efficacy of CBT for chronic obstructive pulmonary disease (COPD; see Baraniak and Sheffield, 2011) reports mixed findings on the outcome for CBT for depression but small effects of CBT for anxiety in COPD. A meta-analysis of RCTs of CBT and problem-solving therapy for depression in people with a range of physical illnesses (Beltman et al., 2010) showed benefits of CBT with similar effect sizes across different physical conditions.

CBT with dementia caregivers

Identifying and managing depression in caregivers is important as it is associated with increased breakdown of care and unhelpful caregiver behaviours (Cooper et al., 2010). NICE (2006) evaluated data from two systematic reviews and 25 trials and concluded that there is evidence of effectiveness of CBT on symptoms of depression and anxiety in caregivers who have clinically significant symptoms. The review also concluded that therapy for the carer can improve the mental state of the person being cared for and delay the move to institutional care. Reframing of negative automatic thoughts appears to be an active ingredient of therapy, at least in reducing caregiver depression and anxiety (Vernooij-Dassen et al., 2011). There are also descriptions of mindfulness-based cognitive therapy (MBCT) used with dementia caregivers (Franco et al., 2010; Oken et al., 2010) and with the person with dementia along with their caregiver (Kemp et al., 2016)

Overall, the evidence for dementia caregiving suggests active interventions are more effective than passive interventions. CBT is most beneficial when targeting specific symptoms of depression and anxiety.

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While psychoeducation improves subjective wellbeing, it is effective in reducing distress only if it is active. Two comprehensive reports have confirmed the efficacy of CBT for caregivers. Funded by the US Veteran's administration, Goy and colleagues (2010) published a systematic review of the evidence base of interventions aimed at non-professional carers (informal caregivers). In the UK, Elvish and colleagues (2012) examined the evidence for psychosocial interventions with caregivers and provided sound recommendations when working with caregivers.

CBT for people with dementia

Evidence for the efficacy of CBT in anxiety and depression in dementia is intriguing and comes from a range of small clinical trials and case studies that suggest that, at least in the mild to moderate stages of dementia, CBT may be efficacious in reducing depression and anxiety (see Orgeta et al., 2017 for review). In the UK, a small trial of CBT reported very promising results (Spector et al., 2015). In the US, a recent development of Problem Adaptation Therapy (PATH) by Kiosses and colleagues (2011) has shown promising results around a 12-session home-delivered intervention based on PST that recruits caregivers as co-therapists. Kiosses and colleagues (2015) carried out a reasonably large RCT of PATH and reported potentially exciting results for a new CBT approach, although the study needs replication and extension as the data only report outcome at 12 weeks' end of treatment and no follow-up. Currently, we are at an exciting stage of development in CBT; there is potential to extend this form of treatment to people facing the often-difficult transition after diagnosis with a dementia.

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Interpersonal psychotherapy

Chapter: Interpersonal psychotherapy

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Introduction

Interpersonal psychotherapy (IPT) is based on the straightforward observation that depression has a negative impact on relationships (Weissman et al., 2000). Fundamental to IPT is the assumption that interpersonally relevant life events increase an individual's vulnerability to developing depression, and depression itself may worsen or, at the very least, maintain interpersonal problems (Hinrichsen and Iselin, 2014). The model does not ignore the biological underpinnings of depression or the role of physical treatments, but it places the emphasis of intervention within the interpersonal domain. IPT is informed by attachment, communication, and social theories (Weissman et al., 2000). Early experiences and unmet attachment needs are seen as important in the aetiology of depression. Interpersonal problems are classified into four categories: complicated bereavements, role transitions, interpersonal disputes, and interpersonal deficits. A role transition may be the loss of a role, e.g. retirement from work, or the acquisition of a new role, e.g.

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becoming a carer for a spouse with dementia. A role dispute is a conflict in a relationship that may occur, for instance, when an older person dealing with ill health resists accepting the practical and emotional support offered by an adult son or daughter.

IPT aims to reduce symptoms of depression by helping patients to better manage interpersonal problems and by improving social functioning. Symptoms are linked to interpersonal events and interactions in order to discover ways to improve communication and repair or build social supports (Ravitz et al., 2013). Understanding the patient's culture is important, and we must grasp how they believe their depression has been caused and how they would usually approach this type of problem. IPT interventions consist of behavioural change methods, enhanced communication analyses, and encouraging expression of emotions, among other techniques. The therapeutic relationship is considered important in IPT (Hinrichsen and Iselin, 2014).

Applications of IPT

Early practitioners of IPT were quick to see the relevance of the model to late-life depression (Sholomskas et al., 1983). It has since been used in post-stroke depression (Finkenzeller et al., 2009) and there is proof of concept of IPT as an intervention for depressed older people with suicidal ideation (Heisel et al., 2015). IPT has also been developed for Internet delivery (Donker et al., 2013).

Treating depression without cognitive impairment

IPT follows a set structure, the plan and time frame being made explicit from the start. Lemma and colleagues (2007) outline the competences necessary for effective IPT (see <http://www.ucl.ac.uk/clinical-psychology/competency-maps/ipt-map.html>). Initial sessions focus on the patient's styles of communication and attachment (secure, avoidant, or anxious) and include a detailed survey of relationships. These not only include family and social relationships but also those with other key people, e.g. professionals. Education on the nature of depression is given with an emphasis on depression as an illness and, in the initial stages of therapy, patients are encouraged to accept the 'sick role' and the limitations their depression places upon them. Identifying with the 'sick role' helps a patient lessen self-blame. Nevertheless, during this phase of treatment, the therapist encourages the patient to address their current problems. Sessions three to 12 use specific techniques to work on the identified foci and sessions 13 and 14 are for review and planning for the future (Stuart and Robertson, 2012). The most common IPT problem with older people is role transition, as late life is commonly a time of both role loss *and* acquisition (Hinrichsen and Clougherty, 2006). Within the theoretical model of IPT, various therapeutic techniques can be employed to tackle the identified problems. These include facilitation of expression of mood, problem solving, and cognitive strategies aimed at the patient's attitudes to roles and relationships. Sometimes directive and practical

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interventions may also be useful, such as help with transport or finances. Fig. 18.1 shows how problem-solving methods may be used in IPT.

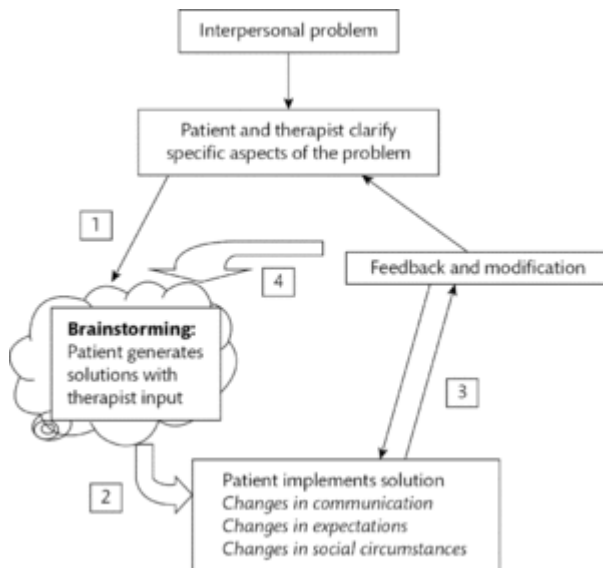


Fig. 18.1
An overview of problem solving in IPT.

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Few adaptations are necessary when using IPT with older people without cognitive impairment. Hearing acuity and educational status should be taken into account and sessions may need to be shortened for medically ill patients. It may also help to involve the spouse or any other significant person in evaluating interpersonal problems, and telephone top-up sessions may be beneficial (Miller, 2008).

IPT can also be provided in group format. Before group sessions begin, the patient receives two individual sessions for assessment and preparation for the group. In group format, psychoeducational aspects of treatment are strengthened and participants can join one another in applying therapeutic techniques, e.g. decision analysis (Scocco et al., 2002), while the forum can provide practical and empathic interactions between group members (Robertson, 2004).

Dealing with grief and loss

Grief and loss are the reactions that may give rise to depression in response to the death of a significant person or people. The therapist's role is to facilitate the grieving process by clarifying the nature of the relationship with the deceased and by helping the patient look for alternative supports and interests. Complicated grief reactions might be

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precipitated by the loss of apparently unimportant figures because of unexpressed grief relating to losses much earlier in life (Frank et al., 1993). IPT aims to help the grieving patient relinquish the attachment to the lost figure, to communicate the loss to others, and to develop new attachments (Stuart and Robertson, 2012). A grief reaction may be for a spouse who has become disabled or has dementia. In this situation, IPT helps the patient maximize the remaining positive aspects of the relationship, grieve for what has been lost, and to give support in making the most of the social network. When working with a patient facing his or her own death, an anticipatory grief approach might be taken to help engagement with the social network and by putting affairs in order.

Dealing with role disputes

Role disputes are interpersonal struggles typically with the partner or other family member and may become apparent when older people suffer disabling physical illnesses. Role disputes both contribute to depression and are made worse by the social withdrawal associated with depression. The therapist's role is to help the patient to understand his or her role in the dispute, link it with the depression, and then to take a problem-solving approach to change aspects of the relationship. It may be that the problem can be overcome if communications are improved, or in some cases it may be that the relationship cannot be repaired. With older adults, it is often preferable to try to bolster a relationship rather than risk a significant loss. For some couples, the potential for role disputes declines as they grow more comfortable together in late life; in others, there is increased interpersonal tension due to illness burden and increased proximity, or caregiving for a dementia spouse. Sometimes role disputes involve ill or financially dependent children or grandchildren (Stuart and Robertson, 2012).

Dealing with role transition

Role transition means a shift in an interpersonal role such as retirement or increased dependency on an adult son or daughter after the onset of chronic illness. The therapist helps the patient to understand the link between the role transition and depression and to look for positive as well as negative aspects of the transition to help the patient develop a greater sense of mastery in the new role. During IPT with older adults, an initial focus of role transition often resolves, only to reveal more long-standing role disputes, often with the spouse (Miller and Reynolds, 2002).

Dealing with interpersonal deficits

Interpersonal deficits (or interpersonal sensitivity) is the least validated of the four problem areas in IPT and is usually avoided as the therapeutic focus if possible. It implies a long-term difficulty in forming interpersonal relationships and may be accompanied by an impoverished interpersonal network. This will include patients with personality disorder but could also embrace those with chronic low-grade mood disorder. As with other problem areas in IPT, treatment does not focus on the early origins of the

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deficits, but rather on ways of reducing social isolation, which may include identifying and reversing unhelpful patterns of relating, or improving assertiveness skills.

Maintenance treatment of depression

After completion of a 16-session course of IPT, further sessions spaced over weeks or months can be provided to try to prevent recurrence of depression. The therapist and patient aim to identify factors likely to be involved in the recurrence of depression, including social deficits and long-standing patterns of interpersonal behaviour (Frank et al., 1993). Therapy is likely to involve a greater number of foci than acute phase treatment and to include a plan for identifying the early warning signs of future episodes of depression. When patients have been depressed for long periods, they may also need help in adapting to being a well person again, which in itself constitutes a role transition.

Treating anxiety

When anxiety is present alongside depression, some authors suggest certain modifications to IPT, such as providing an explanation of anxiety and its impact on relationships and the incorporation of cognitive behavioural strategies (Cyranowski et al., 2005). In the last few years, IPT has also been used in the management of primary anxiety disorders, including post-traumatic stress disorder and social phobia. Intuitively, IPT should help people to overcome some of the social effects of anxiety, such as avoidance and interpersonal sensitivity, and help older adults when anxiety disorders are triggered by retirement or traumatic events (Robertson et al., 2004).

Treating depression with cognitive impairment

When depression is associated with permanent cognitive impairment, the aim of IPT is to help the patient achieve a new steady state of function commensurate with current cognitive ability. The patient is reminded of the abilities that remain intact that could be further developed or enhanced and, when necessary, helped to accept increased dependency on others (Miller, 2008). The therapist may adopt a more active role to steer the patient towards achievable goals. Caregivers, when involved, may benefit from education on the nature of the cognitive impairment and help in understanding their own responses. For instance, they may have been misreading signs of depleted executive function as laziness or contrariness.

Evidence-based guidance on IPT in treating depression and studies of IPT with older people

IPT has been evaluated in a range of psychiatric disorders and most rigorously in depression (Cuijpers et al., 2011; Cuijpers et al., 2016). IPT appears to be more effective in treating depression when used in combination with medication, and is also used in subthreshold depression

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to prevent progression to major depression, and as a maintenance treatment. The UK National Institute for Health and Clinical Excellence (NICE) draft Depression Guideline recommends IPT for the treatment of less severe depression when a focus on interpersonal difficulties is appropriate and cognitive behaviour therapy, behavioural activation, and antidepressant medication have been ineffective or declined (NICE, 2018).

Two of the most influential trials of IPT with older people have been conducted when participants entered the maintenance phase of treatment for depression. These trials examined the effect of IPT with or without antidepressant treatment in participants who had recovered from an episode of depression while receiving a combination of IPT and antidepressant. In the first (Reynolds et al., 1999), participants were relatively young outpatients (60 years or over) who had suffered at least two episodes of depression. In maintenance treatment they received nortriptyline alone, drug placebo alone, IPT alone, or a combination of both treatments. Follow-up was at monthly intervals for three years. The combination of IPT and antidepressant produced the lowest recurrence rate on the Hamilton Rating Scale for Depression and was superior to both drug placebo and IPT alone

In the second study (Reynolds et al., 2006), participants were aged 70 years or over and had more medical illness than in the first study. Some also had cognitive impairment and may have been developing dementia. Half of the participants were in their first episode of depression. They were randomly assigned to paroxetine alone, placebo alone, monthly IPT alone, or a combination of paroxetine and IPT and followed for two years. Randomization was stratified according to number of episodes of depression, use of augmented pharmacotherapy in the acute phase, and degree of cognitive impairment. Combined treatment did not produce lower recurrence rates than antidepressant alone and IPT was no more efficacious than drug placebo. The authors suggest that the cases of depression in this study were more resistant to treatment due to cognitive impairment. Cuijpers and colleagues (2011) concluded that there 'is no doubt that IPT efficaciously treats depression, both as an independent treatment and in combination with pharmacotherapy. IPT deserves its place in treatment guidelines as one of the most empirically validated treatments for depression.'

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Non-pharmacological interventions in care homes, with particular emphasis on the treatment of people with dementia



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Non-pharmacological interventions in care homes, with particular emphasis on the treatment of people with dementia

Chapter:

Non-pharmacological interventions in care homes, with particular emphasis on the treatment of people with dementia

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Introduction

This chapter provides an overview of the non-drug treatments offered to care home residents, paying particular attention to the literature on those residents with cognitive impairment. Depending on age and home type, it is estimated between 52–80% of residents will have some form of dementia (Alzheimer's Society, 2013). It is the unique housing of so many people with complex needs together within communal units that provides the necessity for special attention.

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Context

Care homes in the UK can trace their origins to the sixteenth-century provisions of religious orders, the seventeenth-century Poor Laws and workhouses, and the eighteenth-century infirmaries. By the twentieth century, care of the elderly was regarded as a concern of the State. With the establishment of the NHS and the rise of geriatric medicine in the UK, rapid improvement occurred in services offered to the aged (British Geriatric Society, 2016). Even at this time, however, there were worries that the high numbers of chronically sick older people could seriously hinder the establishment of the embryonic NHS. This latter concern is still prevalent, and was a major reason from the 1980s for the NHS to gradually withdraw its role in the long-term care of the elderly. Today, continuing care provision is chiefly the role of both the private and charitable sectors. According to the Commission for Quality of Care (Oscar Research, 2017) there are over 22,000 care homes in the UK (Scotland 1618; Wales; 1161, Northern Ireland 580), with an average occupancy of 88%. The overarching ethos in care homes is that they are places where people with complex health needs live; it is their home, and quality of life (QoL) matters. Approximately 416,000 people live in care homes (Laing, 2014). This is 4% of the population aged 65 years and over, rising to 16% of those aged 85 or more.

It is important to highlight before proceeding further that in the UK the term 'care home' is a catch-all term used for nursing homes (care homes with nursing care) and residential homes (care homes without nursing care). Care homes with nursing care provide help and assistance with personal care, which is also provided by those without nursing care (residential care homes), but they also have registered nurses and care assistants who provide 24-hour nursing care. In addition to providing general nursing care, many homes offer rehabilitation services, such as physical, speech, and pain therapies, dementia care, and palliative care. The latter homes are for people who are very frail or have complex health care requirements.

This shift in service delivery to the private sector has had major consequences in terms of funding, governance, quality of care, staffing, service provision, and coordination, with respect to 24-hour care provision. Surveys also suggest that the characteristics of people entering private care have been affected by policy changes, with residents entering care being older, more chronically ill, and more cognitively impaired (Peace, 2003). While such profiles have major implications in terms of the treatments required by residents, the trends are not necessarily seen negatively. Indeed, a number of the UK's Dementia Strategies have called for the proportion of people with dementia living in care homes to decrease, seeking to support more people in their own homes for longer (Care Quality Commission, 2017; Alzheimer's Society, 2014). The profiles of the staff caring for this highly impaired, vulnerable group of patients have also changed due to the private sector's involvement, with work forces tending to be more itinerant, less well

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educated, poorly paid, and foreign-born compared to the few remaining equivalent NHS or local authority homes (Peace, 2003). The latter feature is relevant in terms of the effective delivery of non-pharmacological treatments due to the fact that it is the staff who are invariably delivering such treatments, whether formally or informally, via their communication skills (James and Jackman, 2017; Eggenberger et al., 2013).

An understanding of the different needs of residents in care homes, and how interventions may be best tailored to meet them, is essential. Fig. 19.1 maps out a range of needs in a 3-D model and attempts to capture the diversity along three different continua; an axis of good to poor physical health, an axis of good to poor cognitive health, and one for good to poor mental health. While this model does not entirely account for the variations in symptoms of all residents, it highlights the complex nature of people residing in care homes.



Fig. 19.1
Three-axes representation of health

Using this model, it becomes apparent that care homes could be caring for residents who are in good physical and mental health and cognitively intact and residents who are significantly impaired in each of these domains (along with all the people in between). As expected, the needs of people at different points along these continua will differ greatly, as will the mechanisms of providing treatment and support. Indeed, those who are not suffering from a recognized 'condition' (e.g. diabetes, delirium, depression) will not require specific clinical treatments, but active steps will be required to ensure they do not develop the conditions. This is an important point as it suggests that clinical input should be both preventative as well as reactive.

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Table 19.1 highlights common health conditions experienced by older people in care, and some are preventable with the use of appropriate screening procedures, policies, dietary care, and staff training. The items in this table are also triggers to agitation and other problematic behaviours displayed by residents (James and Jackman, 2017). As such, the table reminds us that the axes in Fig. 19.1 are not independent of one another, and a change on one axis may produce changes on the others. For example, take Morris, who was referred to clinical services because of his depression, constant shouting, poor mobility, and cognitive impairment. Following successful treatment of the arthritis in his knees, he became more independent, his mood improved significantly, and he stopped shouting. In Morris's case, the two latter features were both 'reversible' conditions, whereas his dementia was not significantly impacted by the changes. In this case, his cognitive impairment was seen as an 'irreversible' feature.

Table 19.1 Common health conditions observed in residents in care homes.	
Muscles	• Severe cramps • Spasms • Poor coordination • Balance and posture
Skeletal problems	• Arthritis • Osteoporosis • Spinal injuries
Skin integrity	• Rashes • Bruising • Redness • Swelling • Unusual colour
Swallowing/eating	• History of choking or aspiration • Pocketing of food in cheeks • Excessive chewing
Oral and dental	• Gum disease • Dental decay

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	• Ill-fitting denture(s) • Bad breath
Mobility	• Recent falls • Use of mobility aids • Abnormal gait • Ill-fitting shoes
Endocrine (metabolic) disorders	• Hypoglycaemia associated with diabetes • Hyperparathyroidism • Thyroid problems (hypothyroidism & thyrotoxicosis) • Liver cirrhosis • Kidney failure • Rapid changes in sodium levels
Bladder and bowel	• Incontinence • Constipation • Diarrhoea • Frequency • Colour • Odour • Infection
Drug intoxication and side-effects	• Effects of prescribed and non-prescribed drugs
Wound	• Skin tears • Ulcers • Wound discharge • Odour
Pain/discomfort	• Fidgeting, restlessness • Guarding a joint/limb • Grimacing

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	• Calling out • Groaning
Sleep	• Insomnia • Daytime napping • Sundowning • Nightmares • Sleep apnoea
Sensory	• Alterations in vision, hearing, touch • Taste and smell deficits
Blood pressure	• Hypertension • Hypotension
Nutrition/hydration	• Inadequate oral intake • Weight gain/loss • Inability to eat/drink independently • Folate deficiency • Vitamin B12 deficiency

Adapted with permission from James, I.A. & Jackman, L. Treating problems in dementia by understanding biological, social and psychological causes. . In: Ames, D., et al. (Eds). *Dementia*, 5th. CRC Press, Oxford, UK. Copyright © 2017, Informa UK Limited, published by Taylor & Francis.

In many respects, the work of a therapist is to determine what aspects of a resident's presentation are reversible, and then use the correct techniques and skills to reverse them. In contrast, the irreversible conditions often require effective management strategies (e.g. symptom management via drugs, surgery, staff support, specialist equipment, etc.). It is important to note, however, that even when a condition is unlikely to be reversed, the person can benefit from identification and treatment of its psychosocial consequences (see the disability model of dementia, Ballard et al., 2001). Consider Joan, who had experienced a stroke five years ago and which left her with severe right-sided weakness. Unfortunately, the resulting mobility problems prevented her leaving the home to go to the day centre, go out with her family, walk in the home's garden, etc. These were all activities that previously gave her a sense of

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wellbeing. Although the stroke damage is irreversible, the problematic consequences of her poor mobility can be dealt with, and via the correct management she could be able to attend the day centre (training in use of walking frame, assisted-transport to the day centre) and gain access to the garden (installation of a ramp).

In many situations, features on the Mental Health axis of Fig. **19.1** are the easiest to reverse and enhance (i.e. improvements in wellbeing and mood) but they also arguably lead to the greatest distress. For example, depressive symptoms have been found to be associated with disruptive vocalization, one of the forms of agitation often described as difficult to ameliorate in care homes (Dwyer and Byrne, 2000). Underlying depression has an impact on many neuropsychiatric symptoms. It could also be argued that good mental health is the most important status to achieve because if contentment can be obtained, even if an individual has dementia and a serious heart condition, a high QoL is possible. The remainder of this chapter focuses on the methods used to improve people's mental health status. However, it is relevant to state that a key component of non-pharmacological treatments is the use of both adequate screening and treatments for physical conditions (Table 19.1), particularly pain and delirium, which are frequently related to distress, problematic behaviours, and poor mental health.

Mental health conditions

While acknowledging that mental health concerns cover a wide range of diagnostic conditions, for the purpose of this chapter we deal mainly with issues relating to people experiencing cognitive impairment, and in particular those displaying low mood and/or Behavioural and Psychological Symptoms of Dementia (BPSD). These conditions are both seen as markers of stress and distress in dementia (Alzheimer Scotland, 2015). This chapter refers to BPSD as Behaviours that Challenge (BtC), the term used in previous UK national guidance (NICE-SCIE, 2007). We note that the current guidance (NICE, 2018) uses the term non-cognitive symptoms, which is too imprecise for the purpose of this chapter.

Recent randomized controlled trials (RCTs; see Moniz-Cook et al., 2017; James et al., 2017) conducted a survey of mental health conditions with 2185 residents across 63 care homes in the North of England, using the Challenging Behaviour Scale (Moniz-Cook et al., 2001; see Table 19.2). Measured on the Challenging Behaviour Scale, the prevalence of BtC was found to be high, with 87.5% of the 2185 residents exhibiting one or more BtC (Moniz-Cook et al., 2017) (Table 19.2). Only one in eight residents did not display any BtC (N = 274), while 40% displayed ten or more. The high prevalence is in keeping with the majority of studies in care homes with previous rates of 82% (Ballard et al., 2001), 80.5% (Selbaeck et al., 2007) and 91.7% (Bergh et al., 2011); although lower rates of 20% have also been recorded when using more conservative methodologies (Bowman et al., 2004).

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Table 19.2 Table of mental health concerns.	
Mental health concerns	<i>Percentage Occurrence</i> <i>N = 2185</i>
Lack of self care	66
Lack of motivation	50
Lack of occupation	44
Verbal aggression	36
Restlessness	34
Shouting	34
Perseveration	31
Non-compliance	30
Sleep problems	30
Wandering	26
Physical aggression	25
Suspicious	25
Demands attention	24
Interfering	21
Screaming	21
Clinging	14
Self-harm	14
Smearing	13
Manipulative	13
Pilfering or hoarding	12

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Stripping	11
Inappropriate urination	10
Spitting	5
Inappropriate sexual behaviour	4
Dangerous behaviour	4

Source: data from Moniz-Cook E, Woods R, Gardiner E, Silver M, Agar S. (2001). The Challenging Behaviour Scale (CBS): Development of a scale for staff caring for older people in residential and nursing homes. *British Journal of Clinical Psychology*. 40:309-22.

The most frequent behaviours were 'acts of omission' relating to the theme of low affect and 'apathy'. This was consistent with the pan-European study of Aalten and colleagues (2007) which found that apathy was the most common challenge for staff, occurring in 56% of their sample (n = 2808). BtC occurred concurrently, which was also consistent with previous studies (Lyketos, 2007; Volicer, 2007). Such a finding argues against the common clinical practice of treating a particular BtC independently of the rest of the person's presentation (e.g. using risperidone to treat agitation, see Holmes, 2009). Rather, it is more consistent with the notion of the behaviours being manifestations of general distress, calling upon us to undertake more comprehensive assessments of behaviour and identify underlying unifying causes of the full range of the resident's problematic presentations.

Non-pharmacological treatments

International and national reports (Brasure et al., 2016; German Dementia Alliance, 2014; Alzheimer Scotland, 2015) and guidelines (Brechin et al., 2013; NICE, 2018) have highlighted the need for effective non-pharmacological treatments for BtC. Greater use of psychosocial interventions is also consistent with the recent push for giving all people, whatever their status or disability, better access to psychological therapies (NHS England, 2018). However, despite there being a clear need for the use of non-pharmacological treatments, there is little agreement about which ones to use. Cohen-Mansfield's (2001) systematic review of psychological treatments for BtC classified eight types of intervention: sensory, social contact (real or simulated), behaviour therapy, staff training, structured activities, environmental interventions, medical/nursing care interventions, and combination therapies. The study identified 83 non-pharmacological intervention studies via search, although many of these were of a poor standard. Since then, there have been a number of other systematic reviews (Livingston et al., 2005; Ayalon et al., 2006; O'Neil et al., 2011). A meta-review by Vernooij-Dassen

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and colleagues (2010) included 28 reviews related to long-term psychosocial interventions. There were positive effects with behavioural management techniques in relation to mood, behaviour, and physical activities of persons with dementia (PWD). Brasure and colleagues (2016) conducted an extremely comprehensive review that showed only cautious support for non-pharmacological approaches, although it restricted its focus to the treatment of agitation and aggression. More positive findings have been reported in the UK from the WHELD programme (Improving Wellbeing and Health for People with Dementia, see Ballard et al., 2016). This was a five-year programme that undertook three systematic reviews: the first review identified evidence-based training materials; the second examined the evidence for psychosocial treatments for BtC; and the third examined the factors influencing staff use of psychological and social interventions in practice. The findings from the three reviews led the WHELD team to develop care packages that incorporated best-practice interventions. In the subsequent trial, the WHELD treatment package was comprised of: training staff on person-centred care; promoting social activities and interactions; and providing care home staff and general practitioners with updated knowledge regarding the optimal use of psychotropic medications. Using this set of three interventions, the researchers engaged in an RCT with over a thousand residents in 69 care homes. The result was a range of positive findings in relation to resident wellbeing, some of which are yet to be published (Ballard et al., 2016).

Conducting reviews of treatments in this area is rather complex. Firstly, the target 'participants' are far from homogenous; many are physically frail, have dementia and/or anxiety and depression, and are engaging in poorly defined behaviours. Studies address a range of different symptoms of mood or behaviour and outcome measures range widely, which can make the findings difficult to compare. Specific problems relating to conducting research in the area also include difficulties administering a conceptually discrete intervention package.

There is often overlap between the various forms of therapy, and many will include a mixture of environmental, orientation, and staff-training features. Hence, it is difficult to determine which aspect of the package is the change element; such confounds also mean it is problematic comparing the forms of therapy with each other. It is often unfeasible to run double-blind studies due to the rather overt nature of the interventions and difficulty in devising placebo conditions. Despite this, there are several good-quality RCTs and other experimental trials (Table 19.3).

Table 19.3 Non-pharmacological approaches and their evidence base.

Therapies	Systematic Reviews and Empirical Status	Key Articles

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I—Preventative approaches: These are generally designed to promote a positive therapeutic milieu and positive wellbeing. It is suggested that improving people's general levels of contentment serves to improve mood, and reduces anxiety and the incidences of BtC.		
Reality orientation: Uses rehearsal and physical prompts to improve cognitive functioning related to personal orientation.	Spector and colleagues (2002) identified six RCTs. The reviewers concluded there was evidence of improvements in terms of cognitive and behavioural features. RO is now assessed under Cognitive Stimulation Therapy.	Scanland and Emershaw (1993); Woods et al. (2012)
Cognitive stimulation therapy: Uses structured activities to stimulate mental and physical abilities. Usually undertaken in a structured, group format and derived from RO.	Woods and colleagues (2005, updated 2012) suggested that CST had a beneficial effect on memory, cognition, and QoL. Good evidence base for group format, less so for one-to-one packages. Found to be a cost-effective alternative to antipsychotics in reducing distress (NHS III, 2011)	Spector et al. (2006); Woods et al. (2012); Orrell et al. (2014)
Reminiscence therapy: Involves discussion of past experiences individually or in a group format. Photographs, familiar objects, or sensory items used to prompt recall and discussion.	Woods and colleagues (2005b, updated 2009) identified five RCTs, four containing extractable data. The reviewers reported significant results in terms of cognitions, mood, care giver strain, and functional	Bohlmeijer et al. (2003); Brooker and Duce (2000); Lin, Dai, and Hwang (2003)

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	abilities. However, the quality of the studies was perceived to be poor.	
Validation therapy: Based on the general principle of acceptance of the reality of the person and validation of his/her experience.	Neal and Barton Wright (2003, updated 2009) identified three studies, two showing positive effects. However, the reviewers concluded there was insufficient evidence to view the approach as effective.	Schrijnemaekers et al (2002); Feil (1993; 1995)
Psychomotor and exercise therapy: Exercises (e.g. walking and ball games) are used to target depression and behavioural difficulties. The psychomotor interventions are often targeted at enhancing cognitive abilities in addition to physical wellbeing.	Montgomery and Denis (2002) examined the impact of exercise on sleep problems identified one trial that demonstrated significant effects on a range of sleep variables. Teri and colleagues have undertaken extensive work in this area under the generic title of the Seattle Protocols, and shown evidence of effectiveness for tailored and 'fun' activities.	Eggermont and Scherder (2006); Teri et al. (2008)
Multisensory stimulation: Stimuli such as light, sound, and tactile sensations, often in specially designed rooms, used to increase the opportunity for communication and	Chung and Lai (2002, updated 2009) identified a small number of RCTs. A more recent study has shown promising results (Maseda et al., 2014), but was poorly reported. As	Baker et al. (2001); van Weert et al. (2005a,b); Maseda et al. (2014)

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improved quality of experience.	such, to date there is insufficient evidence to view the approach as effective.	
Aromatherapy: Use of essential oils to provide sensory experiences and interactions with staff. The oils can be administered via massage techniques or in patients' baths.	Holt and colleagues (2009) identified two RCTs, but only Ballard et al. (2002) trial reviewed, and found to favour use of essential oils over control oil. More recent trials have mainly failed to find significant effects (AHRQ, 2016).	Ballard et al. (2002); Fujii et al. (2008); Yang et al (2015)
Bright light therapy: Use of full spectrum light to enhance wellbeing, increase activity, and promote day/night sleeping cycles.	Four good quality trials in area. Reviewed by AHRQ (2016), who concluded that only one trial has shown moderate effects (Burns et al., 2009), and this study has methodological flaws. Forbes and colleagues (2014) state there is insufficient evidence at this point in time to recommend its use.	Burns et al. (2009); Forbes et al. (2014)
Music therapy: Includes playing and/or listening to music as a way of generally enhancing wellbeing. Can be used in movement therapies.	Vink and Birks (2009) identified five studies. However, the quality of the studies was poor. As such, the reviewers concluded there was insufficient evidence to view the approach as effective.	Sherratt (2004); Remington et al. (2002)

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Environmental manipulation: use of environmental cues, signage, and appropriate building layout in order to facilitate communication, exercise, and pleasure and to reduce disorientation.	The adaption of environments to meet the needs of PWD has been explored extensively by researchers at the Dementia Services Development Centre (DSDC) at Stirling University. They have produced a number of successful interventions. Handley and colleagues (2015) have undertaken a review of helpful strategies used in hospital settings to improve outcomes for people living with dementia and their family/carers.	Zuidema et al (2010); Day et al. (2000) DSDC (2014)
II—Intervention strategies (formulation-led approaches): These are reactive strategies, responding to difficulties that have already been diagnosed (depression, anxiety) or observed (agitation, shouting, wandering) and the procedures are specifically targeted to intervene with the problem or its causes. These approaches routinely involve the development of a formulation to help understand the triggering and maintaining features of the problem.		
Behavioural management techniques/ Functional analysis (FA): Based on learning theory and utilizing the antecedents and consequences of behaviour to devise and execute interventions. The approach has a long therapeutic tradition and can be applied to all people, no matter	A systematic review by Spira and Edelstein (2006) reported 23 studies. These tended to be of poor to moderate quality, and many were single case design. Moniz-Cook and colleagues (2012) identified eighteen studies with weak but favourable evidence.	Teri et al (2005); Moniz-Cook et al. (2012)

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the level of cognitive impairment.		
Psychotherapies: Adaptions for 1:1 therapy with people with dementia are recent developments, and limited to people with mild dementia. However, use of the underlying principles of CBT, IPT, and psychodynamic approaches are widespread, particularly in programmes aimed at promoting improved carer interactions.	Teri et al. (1997) demonstrated the positive impact of CBT on mood and problem-solving abilities in people with dementia. Teri and Gallagher-Thompson's (1991) RCT revealed significant reduction in depression for both people with dementia and their carers. Scholey and Woods (2003) undertook CBT with seven people with dementia and depression, and identified key themes in such work.	Teri et al., (1991); Miller (2009); James (2010)

The first group of approaches are *preventative strategies* and are generally designed to promote a positive therapeutic milieu and positive wellbeing. It is suggested that improving people's general levels of contentment serves to improve mood, and reduces anxiety and the incidences of BtC. In our discussion of these, we have distinguished between more established and 'alternative' preventative strategies.

The second form of approach is *formulation-led intervention*, which is used when a specific issue requires treatment, for example, a BtC, or disorder (e.g. depression, anxiety). In the case of formulation-led interventions, the procedures are specifically targeted to intervene with the problem or its causes. The formulation-led interventions involve the development of a formulation (i.e. conceptual map) to help understand the triggering and maintaining features of the problem. It is noteworthy that the formulations are not the actual mechanisms of change; they are methods used to obtain information about biopsychosocial features, helping clinicians to target their therapeutic approaches. They lead to care plans, which give precise instruction about what needs to be done. The formulation allows for correct choice of treatments and precise and orchestrated delivery manner to meet the PWD's needs.

Use of preventative approaches

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Preventative approaches are designed to create an atmosphere and environment aimed at promoting the wellbeing of PWD. Many of the approaches in this category could be termed person-centred in that they are designed to (i) support the strengths of PWD; (ii) focus on their difficulties; and (iii) foster psychological health and validate their daily experiences (Brooker, 2007). This section discusses the approaches in descending order of their evidence base, moving from the more established and empirically tested therapies to those methods for which the evidence is weaker.

Established preventative therapies

Reality orientation (RO)

RO attempts to orientate residents to the present via the use of cues (clocks, calendars, newspapers) and/or discussion. The rationale underpinning this strategy suggests that, owing to memory and orientation problems, PWD are often confused, which may lead to social disengagement. However, if PWDs are provided with cues that enable them to engage in what is happening in the 'here and now', they are able to participate in conversations in a more confident and fulfilling way. The provision of environmental cues (signs, picture boards) also has the advantage of assisting residents with dementia to find their way around their setting.

RO used to be one of the most widely used strategies, but in recent years it has become less popular as concerns have been raised about the inflexible way in which it has been practised in some services. There is debate regarding the efficacy of the approach (Verkaik et al., 2005), which centres around claims that RO can remind the participants of their deterioration (Goudie and Stokes, 1989) and that it can lead to repeated confrontations with the PWD (Brooker et al., 2001).

Cognitive stimulation therapy (CST)

CST developed from RO and involves activating residents' remaining cognitive functioning through the use of stimulating activities (e.g. use of physical games, word and number games, everyday objects; see Spector et al., 2006). In its purest form CST is a manualized approach that is run in groups and led by a trained facilitator. Each session follows a general theme, with choices of activities in order to cater to the interests of the group. There are warm-up activities, a RO board (containing information about the group), and often a 'theme song'.

Livingston and colleagues' (2005) systematic review of six studies of varying quality (e.g. Spector et al., 2006; Romero and Wenz, 2001) concluded that this approach showed promise across a range of situations. This view was confirmed in an expert review (Woods, Aguire, Spector, and Orrell, 2012), which concluded that there is consistent support for CST, over and above the effects of medication in relation to improvements in QoL. It also demonstrates cost effectiveness due to the

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fact that it can often be performed in a group setting (Knapp et al., 2006). There is ongoing work examining the longer-term effects of CST, referred to as *maintenance CST*. For example, in a trial consisting of 26 weekly sessions of extended CST there were significant continued benefits found in terms of some variables (although not all), such as QoL (Orrell et al., 2014).

Reminiscence therapy (RMT)

RMT involves residents reliving past experiences, especially those that might be positive and personally significant (e.g. family holidays, weddings). It can be delivered as a group therapy or with individuals (Kaiser and Eley, 2016) and may utilize photographs, art, music, etc., to provide stimulation. RMT is seen as a way of increasing levels of wellbeing, providing pleasure, and boosting cognitive stimulation.

When working with PWD in care facilities, care staff and families are often encouraged to jointly construct historical reviews of the residents' lives (i.e. life stories). Life story work is helpful in promoting attachments between staff and residents, particularly in cases where residents have poor communication skills. Evidence supporting this comes from work undertaken by Subramaniam and colleagues (2014), whose qualitative findings showed that care home staff reported having a greater knowledge and more positive attitudes towards dementia after the use of life story books.

However, while there is growing evidence that RMT is an effective treatment for older PWD (Testad et al., 2014; Cotelli, 2012; Subramaniam and Woods, 2012), studies continue to show mixed results for its effectiveness within care home settings (e.g. Gudex et al., 2010, Hsieh et al., 2010). As a result, careful consideration is needed about the aims for its use.

Validation therapy (VT)

VT was developed to address the perceived lack of flexibility of the RO approach with PWD. Its originator Naomi Feil (Feil, 1993; 1999) suggested that some of the features associated with dementia, such as repetition and retreating into the past, were active strategies to avoid stress, boredom, and loneliness, and were most often used by people with moderate or advanced dementia. She argues that the PWD can retreat into an inner reality based on feelings, rather than intellect, as they find their present reality too painful. VT therapists thus attempt to communicate with the PWD through empathizing with the feelings and hidden meanings behind their confused speech and behaviour. It is the emotional content of what is being said that is important, rather than the person's orientation to the present.

It is, however, suggested that therapists can become too focused on confused communication and fail to identify simple explanations such as pain or hunger. Neal and Barton Wright (2003) evaluated VT's

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effectiveness across a number of controlled trials employing cognitive and behavioural measures (e.g. Finnema et al., 1998, 2000). They concluded that, despite some positive indicators in terms of depression (Toseland et al., 1997), its efficacy remains equivocal. Subsequent small controlled studies (Deponte and Missan, 2007; Tondi et al., 2007) have found a reduction in behavioural disturbance and so this approach may be helpful in addressing these signs of distress.

Environmental modification

Environmental modification is based on the premise that, by developing a psychosocial understanding of behaviour and its meaning for the person, the environment can be changed to meet his/her needs. Evidence suggests that modifying environments can be effective in improving wellbeing and reducing unwanted behaviours for people with mild or severe dementia (Bowie and Mountain, 1997). The use of colour and structure in an environment can help with orientation (Gibson et al., 2004). Designing an environment with a more home-like atmosphere with good lighting and some environmental stimulation can reduce unwanted and agitated behaviours (Day et al., 2000). Access to safe gardens and outdoor spaces is also beneficial and opens up the possibility to develop horticultural type therapies with residents.

In recent years there has been a growing tendency in some care facilities to recreate artificial environments (e.g. pubs, bars, cafes, market places) with the notion that this may reduce levels of agitation and increase levels of interaction between residents. Critics have warned, however, that these artificial environments should always sell/offer items for sale consistent with their proposed purpose (Mental Health Foundation (MHF), 2016). The MHF report on deception in dementia care, considers that 'pubs that do not provide drinks are likely to further confuse and agitate PWD'. A comprehensive evidence-base has yet to be established in this area, although a number of controlled studies (Livingston et al., 2005) and a larger number of non-controlled studies have shown environment and design to be important (Hulme et al., 2010; Zuidema et al., 2010).

Psychomotor therapy

Psychomotor therapy, sometimes referred to as activity therapy, is a varied group of action-based activities, such as sport or drama. Cohen-Mansfield and colleagues (2010) demonstrated the positive impact of a range of such activities for residents in care. The findings revealed that the most enjoyable tasks were those that involved engaging with living things (people, real baby, animals), followed by tasks involving some form of social simulation (use of dolls, simulation presence videos). However, when length of engagement was assessed (i.e. length of time spent on task), the residents spent longer on tasks that mimicked work-like activities (stamping envelopes, sorting jewellery, folding towels). These results are likely to have important consequences in terms of the sorts of

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activities carers can use to help occupy PWD in order to enhance well-being, increase self-worth, and relieve boredom.

Studies of specific action-based activities have provided mixed results. Studies of drama and movement groups have showed positive outcomes in terms of increased communication (Hokkanen et al., 2003) and moderate benefits in terms of relaxation and orientation (Wilkinson et al. 1998). The therapeutic use of touch occurring with activity programmes has also been found to reduce disruptive vocalizations (Woods et al., 2005). A good quality-controlled trial by Montgomery and Dennis (2002) showed a positive impact on a range of sleep variables.

Despite these findings, two better quality-controlled trials conducted in the area failed to find significant differences in terms of depression and apathy when compared to treatment as usual (Hopman-Rock et al., 1999; Dröes, 1991). Of further concern was the attempted systematic review by Karkou and Meekums (2017) on dance movement therapy, and their conclusion that none of the available studies were sufficiently robust to meet their inclusion criteria.

Exercise

The benefits of moderate exercise in relation to chronic degenerative disease is well established (Heyn et al., 2004). Vogel and colleagues (2009) has reviewed aerobic exercise health benefits, which include a reduction in cardiovascular morbidity and mortality, optimization in blood pressure and lipid profile, improved executive function, cardiorespiratory fitness, and insulin sensitivity (Colcombe and Kramer, 2003). Other benefits, such as a slower rate of decline of activities of daily living, have been shown to result from a simple exercise programme, one hour twice a week (Rolland et al., 2007). Exercise has also been shown to increase older people's mood and confidence (Young and Dinan, 1994; Singh et al., 2005; Guzman et al., 2016), but not necessarily reduce BtC or improve cognition (Forbes et al., 2015).

One of the concerns in the area has been how to engage people in exercises that they would find meaningful and fun. Guzman's work has attempted to achieve this via the use of dance (Guzman et al., 2016), and achieved benefits on a range of mood and psychosocial factors. The largest body of work to date has been The Seattle Protocol programme (Teri et al., 2008). This is a series of systematic, evidence-based approaches focusing on the importance of making regular exercise a pleasant activity for both the participants and their caregivers.

Multisensory therapy

Multisensory approaches usually involve using an activity room that has been designed to provide several types of sensory stimulation, such as light, texture, smell, and sound. The use of these resources is tailored to the individual person and therefore all of the forms of stimulation are not necessarily used in one session. Some of the reported benefits for those

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with more advanced dementia include a reduction in aggressive behaviours, apathy, and depression and an increase in interaction and signs of wellbeing (van Weert et al., 2005a; van Weert et al., 2005b). However, individuals differ in their response to this treatment, with some studies failing to find an effect and some obtaining a negative one. The latter findings highlight the need for individualized assessments and planning (Hope, 1998).

It is also possible to bring sensory experiences into the daily lives of PWD through the use of interesting and stimulating decorations, colour schemes, and textures in the environment, and the selection of personal care items, such as scented toiletries (Wenbourn, 2003). Chung and Lai (2002) reported that, overall, the findings were inconclusive. However, more recently, Verkaik and colleagues (2005) suggest that multisensory approaches are particularly effective in the treatment of apathy and depression both in 24-hour care and in the community.

Alternative preventative psychological strategies

Aromatherapy

The two main essential oils used in aromatherapy for dementia are extracted from lavender and lemon balm, and can either be inhaled or applied via massage. Early controlled trials showed significant improvements in agitation symptoms with excellent compliance and tolerability (Holmes et al., 2002; Ballard et al., 2002), but both these studies have flaws and therefore the findings must be treated with caution. More recent studies have found rather mixed results (Fujii et al., 2008; Yang et al., 2015), similar to that arrived at by Forrester and colleagues (2014).

Light therapy

Light plays a big role in maintaining our circadian rhythms and light therapy can be used to reset these rhythms when they are disrupted. The use of light therapy for Alzheimer's disease, and related dementias, has been shown to help with sleep disorders and agitation, which may or may not be related to tiredness. The benefits can be experienced by both PWD and their carers, with both experiencing more sleep (Figueiro et al., 2015). Burns and colleagues (2009) found that dementia patients who sat in front of a bright light (10,000 lux) for two hours each morning slept an average of 40 minutes longer and slept more deeply than usual. A control group who sat in front of a 100-lux light slept only about eight minutes longer. This tendency was most evident in the winter months.

Riemersma-van der Lek and colleagues (2008) reported that light therapy alone had a modest benefit in improving some cognitive and non-cognitive symptoms of dementia. However, the best effects were observed when it was used alongside the administration of melatonin. The notion being that both treatments were synchronizers of the circadian system.

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Forbes and colleagues (2014), however, recommend caution. They suggest there still is insufficient evidence to recommend light therapy for improving the wellbeing of people with dementia.

Music therapy

The poor quality of studies on music therapy has been noted (Vink et al., 2009), but nevertheless, it has long been accepted within the scientific literature that music can have a profound effect on people's mood and wellbeing (Sherratt et al., 2004). Music is also considered useful in reducing unwanted behaviour and improving communication, particularly when tailored to people's taste. Remington and colleagues (2002) showed increased levels of wellbeing and reduced agitation via using calm music and hand massage. Significant effects were found between music alone and the no-music conditions.

A sustained music therapy programme over 30 weeks has also demonstrated a reduction in BtC scores, in particular, reductions in agitation, delusions, anxiety, apathy, irritability, aberrant motor activity, and night-time behaviour disturbances, with improvements maintained at one-month follow up (Raglio et al., 2008). There have also been reported improvements in depressive symptoms through participation in reminiscence-focused music groups (Ashida, 2002) and improvements in communication and irritability when engaged in structured playing of music (Suzuki et al., 2004). Further, it is worth mentioning Sally Magnusson's work, and her charitable organization Playlist for Life. Sally's account of her discovery of the power of music in relation to her mother's dementia is both illuminating and inspiring (Magnusson, 2014). As with all strategies, caution is required when using this approach, as music can cue problematic memories too (e.g. music of the 1940s reminding people of wartime losses).

Art therapy

Art therapy (drama, model making, drawing, and painting) is a treatment in which people have the opportunity to explore new skills (Mottram, 2003) and thereby enhance their self-esteem. In the case of PWD, art therapy has been shown to provide meaningful stimulation, improve social interaction, and raise levels of self-esteem (Killick and Allan, 1999). While many anecdotal studies suggest that this may be an activity that promotes wellbeing, there is limited evidence of its impact on specific conditions or of longer-term benefit when sessions stop.

Animal-assisted activities

Animals introduced into nursing homes as regular visitors or as care home pets have been shown to have positive effects, including reducing blood pressure, agitation, strain, tension, loneliness, and increasing life expectancy (Churchill et al., 1999). Short-term interactions with dogs have been shown to increase social interaction with, and between, older people with mental impairment (Greer et al., 2001). These forms of social

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contact have also proven beneficial in the treatment of BtC (Zisselman et al., 1996). The use of a fish tank in a dining area has been shown to reduce aggression and enhance the nutritional intake of home residents with dementia (Edwards, 2004). Looking after hens has also been shown to have benefits (Cook et al., 2013), with a large grant being awarded to Equal Arts UK to roll out its HenPower project. It aims to provide care homes with the support required to host hen-keeping-related activities onsite as a means to encourage residents to engage in positive social interactions (Rippon and James, 2017). The ethos of the HenPower project is also to support frontline care staff to deliver meaningful activities for the residents related to the hens (caring, nurturing hens, collecting eggs, baking). However, the welfare of human and animal participants needs to be considered in any programme and helpful guidance is now becoming available (Lefebvre et al., 2008).

For situations when live animals are not appropriate, researchers have investigated the ability of robotic animals to provide companionship and increase QoL in nursing home residents. Banks and colleagues (2008) examined the interactions of residents with Sony's robotic dog 'Aibo' and found that Aibo and a live dog reduced agitation and were equally effective in doing so. Similarly, Libin and Cohen-Mansfield (2004) have had promising pilot results with a robotic dog. There is also promising work occurring with the use of a robotic seal 'Paro' (<http://www.parorobots.com/>), although the evidence for this item currently remains limited.

Using dolls and toys

The use of dolls and toys in care settings is not new (Libin and Cohen-Mansfield, 2004), but has only recently been studied in a systematic manner (Alander et al., 2015; Mitchell, 2016). Investigations have involved the introduction of dolls and teddy bears into care homes following a standard format (Mackenzie et al., 2006). Typically, staff are given information and guidelines on their use prior to their introduction (Mackenzie et al., 2007). The findings from these investigations have been favourable for both residents and staff (Mackenzie et al. 2006; James, 2015). However, this approach is controversial and an unresolved debate within the *Journal of Dementia Care* (Mackenzie et al., 2006, 2007) has demonstrated resistance to the technique because it can be viewed as 'patronizing' and promoting 'infantilization'. A full review of the field has recently been undertaken by Mitchell (2016).

Tool box approaches

Some of the above strategies have been presented as stand-alone techniques, but it is evident that often carers combine them and use them in non-standard ways. A good example of this is the various forms of 'tool-box' techniques (Thwaites and Sara, 2008). This widely used approach involves creating an individualized box of items for each person, containing personalized material (e.g. photographs, postcards, camcorder

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recordings of family scenes or voices, items of clothes, ornaments, relevant maps, aromatherapy oils). Carers, particularly care staff, can use the items in the box to stimulate and communicate with the individual, learning more about the person's history and promoting positive reminiscence.

Summary of preventative approaches

Overall, the evidence base for the preventative approaches is variable. The two main reasons for such an equivocal picture are (i) methodological problems associated with undertaking psychosocial research, and (ii) a lack of clarity related to treatment goals.

Methodological problems

Some of this variance is due to the fact that traditional research methods, especially RCTs, are often inappropriate or unfeasible for non-pharmacological interventions with people with dementia (Cohen-Mansfield, 2016). It is also due to the way in which the interventions are delivered. Owing to their preventative nature, they are frequently delivered to a wide range of residents, each on a different stage on the 3-D continua discussed earlier. They are often delivered to groups of people for short periods of time (e.g. one hour) and undertaken infrequently (e.g. once a week). The interventions tend to be available at times that are convenient for the therapist and the care home, as opposed to the residents. Finally, the people with dementia are often entirely dependent on staff to access the interventions (Lawrence et al., 2012) and there may be residents who would benefit but who are not encouraged to attend. As a result, the interventions are rarely truly person-centred as they are not focused on the needs of the residents. Inevitably, this means that some residents will not benefit from the intervention because it is not meaningful to them or delivered at the right time. If we view the preventative interventions in this way it is probable that many resources (e.g. resident time, staff time, therapist time, money) are spent delivering interventions in a way that is counterproductive to the positive benefits we seek.

Lack of clarity related to treatment goals

In the rush by clinicians to find alternatives to medication, many have sought (unsuccessfully) an approach that was a non-pharmacological panacea—an approach that aided well-being, improved affect, and reduced BtC—the equivalent of a 'magic bullet'. Hence, some of the poor efficacy reflects a lack of clarity in terms of the treatments' specific outcomes. From the current authors' perspective, and our review of the area, we believe that the above treatments were generally good at improving wellbeing, but were less consistently successful at improving cognitions, clinical affective disorders, and/or BtC. And such a conclusion would appear to make theoretical sense because, in general, the treatments' various mechanisms of change were not designed to target these clinical features. For example, very few of the studies ever specified

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how exactly RO, CST, aromatherapy, or doll therapy, etc., were supposed to reduce vocal aggression, sexual disinhibition, and shouting, or improve cognitive skills.

In conclusion, the mixed results indicate that the approaches do have value for some people and if we could change the way we deliver them we can maximize their value to residents by ensuring that they are delivered to the right people, in the right way, at the right time, for the right purpose. To do this we need to understand the needs of each individual.

Use of formulation-led interventions

This section discusses a number of formulation-led approaches. Here, typically a condition has already been observed (depression, problematic behaviour) and the formulation-led intervention is specifically targeted at its causes. These interventions routinely involve the development of a formulation (i.e. a descriptive account of the problem in relation to the person and her past) to help understand the triggering and maintaining features of the condition (James, 2010). First it describes some standard psychotherapeutic approaches (Cognitive Behaviour Therapy (CBT), Interpersonal Therapy (IPT)) where the use is limited to those with mild impairment (James, 2010). It then covers therapies that can be used with all presentations, even with cases of severe dementia (behaviour therapy (BT) and needs-led frameworks).

The function of the formulation of the standard psychotherapies varies according to the type of therapy. CBT and IPT formulations are designed to help 'clients' gain a better understanding of their problems; this requires the clients to have a degree of insight into their difficulties and the ability to initiate change with respect to their behaviour. In contrast, BT and the needs-led frameworks employ formulations as vehicles to enable carers to gain a better understanding of the PWD's difficulties. This is particularly important because, in cases of severe dementia, it is the carers who are required to carry out the interventions.

Standard psychotherapies

Over the last ten years there has been an increasing interest in using CBT and IPT with older people, including those with cognitive impairment (James, 2010; Miller and Reynolds, 2007). In relation to PWD, these therapies are used in cases of low mood, anxiety, or when the person retains some insight and problem-solving abilities.

Cognitive behavioural therapy (CBT)

CBT examines people's distress within a cycle of thoughts, feelings, physical sensations, and behaviours. Teri and Gallagher-Thompson (1991) reported positive findings from a clinical trial of CBT with people in the early stages of Alzheimer's disease. Single-case and group CBT have also

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been used by other researchers with some favourable results (Koder, 1998; Kipling et al., 1999; James, 2010).

Interpersonal therapy (IPT)

IPT examines the person's distress within an interpersonal context. People are encouraged to look at how important relationships have changed since they have become distressed, and they are also asked to examine their communication styles to see if they can be improved. Such an approach is particularly relevant for those therapists who see BtC as a communication strategy in a form other people find socially unacceptable. For example, a person with poor verbal skills who is unable to ask for food may snatch something from someone else's hand because she is unable to ask for the item by name.

There is some overlap of IPT with the person-centred work of Kitwood (1997) and Stokes (2000). There is good empirical evidence for this form of treatment with older people (Miller and Reynolds, 2002); it has only recently been applied in the area of dementia (James, 2010; James et al., 2003; Miller and Reynolds, 2007; Miller, 2009). Yet, owing to the demands IPT places on insightfulness and the ability to reflect, its use remains rather limited in treating PWD.

Carer-centred, person-focused approaches

The following approaches can be employed for a range of clinical presentations, even in situations where residents have either poor communication skills and/or poor insight; thus, these methods are suitable for working with people with severe dementia. The key reason for their suitability with this group is that, although the focus of the treatment is directed at the PWD, much of the actual work is done via carers. Working with these interventions therefore requires a systems approach, whereby much of the success depends on supporting the carers to deliver the therapy effectively. For this reason, the approaches are termed 'carer-centred, person-focused' (James and Jackman, 2017).

Behaviour therapy (BT)

Behaviour therapy requires a detailed assessment period in which the triggers, behaviours, and reinforcers (i.e. the ABC model: antecedents, behaviour, and consequences) are identified and their relationships made clear. This process is frequently referred to as a *functional assessment* (Gormley et al., 2001; Moniz-Cook et al., 2012). The therapist will often use a chart or diary to gather information about the manifestations of a behaviour (B) and the sequence of actions leading up to it (A). The reactions to the behaviour (C) are also studied because they frequently serve to either increase or decrease the likelihood of the action occurring again. Such monitoring helps to identify the function of BtC, and the accurate observations are essential in generating better hypotheses. For example, consider the case of Polly, whose continual shouting was initially attributed to arthritic pain. The functional assessment revealed that she

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only shouted in the presence of men, indicating some fear or anger associated with males. This meant her painkillers could be stopped, which relieved her constipation, and the new data allowed the therapist to focus on her issues with men, enabling her therapists to go on to develop a more appropriate intervention.

Teri and colleagues (2005) developed and conducted an 11-session training programme to teach 41 carers of individuals with dementia how to manage agitated behaviour using functional analysis-based behavioural interventions in their home environment. During sessions, carers worked with a therapist to define problem behaviours, complete and interpret functional analyses, and develop interventions. The review of the training programme presented four case studies to illustrate its effectiveness. The antecedents to the four participants' agitation were found to be:

1. Lack of activity
2. Confrontation over confused statements
3. Inactivity specifically at dusk
4. Lack of social attention due to caregiver competing tasks, respectively.

Consequently, antecedent control interventions were designed specifically for each participant (i.e. providing appropriately tailored activities). For one participant, the interventions resulted in the elimination of verbal and physical aggression, and the numbers of agitated and aggressive behaviours also dropped in the other three participants. Unfortunately, no data were presented and only limited qualitative feedback from the participants was reported as an outcome measure, making it difficult to interpret how successful the interventions actually were.

The efficacy of BT has been demonstrated in the context of dementia in several studies (e.g. Spira and Edelstein, 2006). A rigorous review by Moniz-Cook and colleagues (2012) identified eighteen trials, the majority of which were from family care settings, rather than residential care settings. For the primary outcome of frequency of problematic behaviours, only ten studies (n = 1140 participants) had usable data. They concluded that, while functional analysis showed promise, it is too early to provide an indication of its effectiveness. This is because the evidence rests largely on a handful of studies for which the actual effects are unclear, since the intervention tended to be delivered within broad multicomponent programmes of psychosocial interventions.

Positive behaviour support

A recent addition to field of behaviour therapy is positive behaviour support (PBS). PBS is not a technique or therapy, but a formulation-led intervention that uses applied behavioural analysis (ABA) as its predominant theoretical model. Originating from the learning disability field, where it is seen as best practice for the treatment of challenging behaviour (NICE, 2015), it is gradually being adopted across other

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specialties, e.g. child, forensic, personality disorders (see Clinical Psychology Forum, 2017). We are currently examining its use for BtC for PWD, and it clearly has much to commend it. However, the application of the ABA feature, which is essential, is somewhat problematic with this specific clinical population owing to problems to do with memory, learning, and insight (James and Reichelt, 2017).

Needs-led therapies

These approaches have often been developed specifically for the treatment of BtC. Currently there are a number of conceptual models that examine cases of BtC in terms of people's needs (Cohen-Mansfield, 2001; James, 2011; Aberdeen, 2015; Dexter-Smith, 2007, 2010). These frameworks typically involve obtaining two types of information: (i) background features (history, premorbid personality and coping style, cognitive status, mental health status, physical health status, environmental and contextual status), and (ii) a comprehensive description of the problematic behaviours—a functional assessment. Putting these two types of information together provides a stronger foundation upon which to accurately identify the person's needs. Bird and colleagues (2007) have provided numerous case examples of the benefits of this methodology. More recently, Bird has undertaken a controlled study that illustrates the efficacy of his work (Bird et al., 2009). Holle and colleagues (2016) carried out a systematic review of individualized formulation-led interventions that identified 14 formulation-led interventions and 37 studies that employed individualized interventions, mainly in the care home sector. The reviewers found positive findings in terms of PWD outcomes in nursing homes, while the evidence for staff outcomes was less promising. The results for the own-home settings were also positive, but the findings related to only one trial.

The present authors currently work in NHS services in which specialist teams employ needs-led models across all the care homes in their localities ($n > 210$ homes, James and Jackman, 2017). The use of specialist teams who work exclusively with people displaying BtC is relatively uncommon, but successful teams exist in the North East of England (CNTW Behaviour Support Services), Dumfries and Galloway (IDEAS team), and in the Northern Health and Social Care Trust, Northern Ireland. These teams are multidisciplinary, with the latter two containing members from four or more professions. Each of the teams employ their own conceptual frameworks (i.e. the Newcastle model, CEASE, CLEAR), but essentially all view BtC as a communication of an unmet need. Each team works with staff to help them develop a formulation of the person's needs and develop a person-centred care plan (James and Moniz-Cook, 2018).

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Staff training

As demonstrated, staff are a vital piece of the jigsaw in delivering good care in homes. De Vugt and colleagues (2004) showed that some care-giving attitudes and behaviours were associated with incidences of behavioural problems. For example, caregiver impatience, irritation, and anger towards residents were more likely to result in greater resident agitation. In terms of training, the methods of staff education have been varied and involved broad ranging teaching programmes (Burgio et al., 2002) and the use of helpful tools like Dementia Care Mapping (DCM: Kitwood, 1997) and the VIPS care model (Brooker, 2007). These frameworks assess the activity and level of wellbeing from a resident's standpoint, and provide information about caregiver interactions—from which action plans for care improvement can be developed. The DCM tool also acts as an audit of person-centred practice and has been used with positive results in some studies and had a more equivocal impact in others. The fact that it can be both intervention and outcome evaluation creates an obvious confound, but it has good face validity and is well received by practitioners (Brooker, 2007).

In general, evidence shows that staff can be trained to deliver better care (Opie et al., 2002; Schrijnemaekers et al., 2002), but the effects do not tend to generalize across care activities and they tend to fade with time. This was supported in a study by Moniz-Cook and colleagues (2017) that trained staff in the development of person-centred individualized care plans. There was no improvement in the number or frequency of problems, but the homes that received the training did report less difficulty in managing the behaviour. However, these effects were not maintained at one-year follow-up. Programmes that have taken a broader organizational focus in implementing person-centred care in combination with training and mentoring have been shown to have some benefits on medication use in the Focused Intervention Training and Support Programme (Fossey et al., 2006; Fossey and James, 2008; Brooker et al., 2016) and some aspects of QoL in the VIPS model of care (Brooker, 2007) and Enriched Opportunities Programme (Brooker, 2011). Individual care home groups have also implemented their own programmes of organizational and cultural change; for example, the PEARL programme (Baker, 2009) uses a cycle of audit, training, and organizational change to achieve clearly defined standards of care. The most comprehensive review of the area from a UK perspective comes from Surr and colleagues (2016) in the 'What Works' Project. In a sophisticated breakdown of aims and targets, the researchers examined the nature of the training required to achieve good outcomes for both clients and staff.

In terms of client outcomes, their preliminary findings suggest the following;

- One should use face-to-face delivery, and engage in discussion and activities that support the application of learning to clinical work.

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- The training material should be delivered by an experienced trainer who can respond to clinically relevant questions.
- The training should last over one hour, preferably longer.
- The training sessions should be designed for a specific type of service/setting (ward, care home, type of clients).

In contrast, to achieve improved staff outcomes the requirements are:

- Training of a long duration (8+ hrs total, broken down over time), and
- The use of a structured tool or manual to assist with the application of the learning (e.g. FITs, Fossey and James, 2008).

We endorse the 'What works' findings, and once again await the more detailed information that will come from the forthcoming publication of the study. In particular, it is likely that the role of ongoing supervision will be shown to be important in developing and maintaining staff skills and learning.

Discussion

The evidence strongly suggests that individual case-specific formulations, which identify the needs of the individual and lead to the development of person centred care plans, is needed in order to deliver effective psychosocial interventions in care homes (Moniz-Cook and James, 2017; James and Moniz-Cook, 2018). Having reviewed many of the treatments currently available, it is worth highlighting the commonalities between the various interventions. From our perspective, and an examination of the *modus operandi* of many of the treatments, it appears that good communication skills and an ability to interact positively are key to success. This is because many residents in care homes find it an isolating experience due to a combination of the losses experienced (social networks, familiar environment, routines) and cognitive problems (memory and orientation) resulting from dementia. Therefore, when a staff member or therapist engages with a resident using activities, photographs, music, an animal, doll, massage, etc., the individual's level of interpersonal contact rises considerably. For many residents this results in an increase in mood and wellbeing.

More specifically, we believe that the various treatments that were successful either met or enhanced one of the following fundamental needs: physical comfort and freedom from pain; perception of safety; positive touch; love and belonging; esteem; control over environment and possessions (freedom); fun; and occupation and exploration (James and Jackman, 2017). The successful interventions also tended to utilize verbal and non-verbal memories, often in multisensory formats. Yet, fundamentally their success depended on *how* the interventions were delivered rather than the actual *structural* features of the intervention (for example, whether it was RO, dolls, or aromatherapy). Indeed, we

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suggest that the relevance of *how things are delivered* rather than *what was delivered* also accounts for much of the inconsistency in the literature.

Related to the notion of 'how to' is the current focus on the enhancement of staff communication skills. The ability of each member of staff to encourage, negotiate, and de-escalate during everyday interactions is key to the wellbeing of residents, and crucial in preventing BtC and maintaining the safety of others. Two of the most comprehensive programmes in the UK currently are PACTM (Snow, 2012) and CAIT (Communication and Interaction Training; James, 2015; James and Jackman, 2017).

This chapter has also shown that there is a general move towards more person-centred and staff-centred foci of care. Through the use of such perspectives, greater attempts are now made to understand the individual's experience of his/her problem within an intrapsychic, interpersonal, and organizational context (Bond and Corner, 2001). In a large survey of three different types of Japanese care facilities, Onishi and colleagues (2006) found that the incidences and forms of problematic behaviours differed across settings. The carers' abilities to cope with the behaviours also varied. From their findings, the researchers suggested that such systemic knowledge of the resilience of such settings was crucial in determining the appropriateness of placements and transfers. Therefore, it is important to recognize how the context of PWDs' relationships with family and caregivers affects both the individual with dementia and their caregivers. Such a view emphasizes the need to work with all of the systems involved in the resident's care (families, professional carers, organizations, etc.). Indeed, care staff and families are integral to the treatment strategies and are essential in obtaining valid and reliable information and constructing appropriate formulations and interventions.

Conclusion

People living in care homes present with a variety of complex needs. A host of non-pharmacological interventions exist but the evidence base for them is variable; where the evidence is strong, the interventions are rarely implemented widely in care home settings (Lawrence et al., 2012). Individualized formulation-led approaches are evidence based and offer the best way to meet the varied and complex needs of care home residents. However, the fact that care homes in the UK tend to be large environments looking after a number of people makes this a challenge. The care homes primarily sit within the private sector, but local authorities and the NHS fund a large proportion of placements. The current financial pressures on local authorities and the NHS have reduced the fees paid to care homes, which, in turn, reduces the resources they have available. Providing adequate care to such a vulnerable section of the community is resource intensive. If, as a society, we are to provide people in care homes with the care and treatment they

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deserve, it is essential that we continue to identify the active ingredients of successful interventions to ensure we develop care plans that match unmet needs, personal abilities, preference, and the environment (Cohen-Mansfield, 2016). This will give us the best chance of providing care that is both cost effective and meets the needs of residents.

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Principles of service provision in old age psychiatry

Chapter: Principles of service provision in old age psychiatry

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Introduction

Support for mental health in older people can be considered as having two main components. The first of these is the general question of how mental health needs in this section of the population are to be met, which includes public health, primary care and other general health and social care services. The other area is the organization of specialist mental health services for older people. Hopefully, too, there is some co-ordination between these two components, so that older people have appropriate access to services that meet their needs.

The nature and extent of mental health services for older people is highly variable, not only across the different countries of the world, but also within individual jurisdictions. In many countries, separate old age psychiatry services do not exist; nonetheless, even a generic mental health service will need to plan how it responds to the particular needs of older people, especially those with dementia, depression and/or medical

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comorbidity. Ageing populations are a truly global issue, so how mental health services respond to older people is increasingly important.

Where dedicated old age psychiatry services do exist, there are sometimes variations in the scope of their work, and there are frequent changes in how they are configured, for example, due to changes in health service structures or funding. Sometimes these changes are so radical as to include the disappearance of the service as a separate entity, even though the expectation is instead for an *increased* demand for specialist services because of the increasing numbers of older people.

Therefore, this chapter focuses on the principles that underlie services, rather than on the detail, partly because the situation will vary in different parts of the world but also partly because the way services are organized will continue to change, rendering anything too detailed obsolete in a short space of time. Furthermore, several other chapters in this book cover specific aspects of service delivery and these will be referred to where appropriate. This chapter also largely focuses on the UK—specifically England. However, many of the general issues are global and also, as the UK has been one of the leaders in developing service models for old age psychiatry, it is likely that what happens there will be of interest to readers internationally.

History

It is generally accepted that old age psychiatry originated in the UK. The earliest traces of the specialty are to be found in the early 1940s (Hilton, 2005b). Before the Second World War, there was virtually no interest in older people's mental or physical health issues, most conditions being assumed to be degenerative, 'senile', and not amenable to treatment. By the early 1940s, there were large numbers of older people with mental disorders in hospitals like the Royal Edinburgh Hospital and Tooting Bec in London. Felix Post, first working in Edinburgh, and encouraged by Professor Henderson, published one of the first clinical studies of mental disorders in old age (Post, 1944). Aubrey Lewis, in London, was also highly influential, for example addressing the Annual Meeting of the Royal Medico-Psychological Association in 1945 (Lewis, 1946) and being active through the Mental Health Standing Advisory Committee of the new National Health Service (Hilton, 2005b).

Several accounts are available of further developments of old age psychiatry (e.g. Hilton et al., 2010). Important advances included pioneering clinical studies, especially Post (1962), his seminal textbook (1965), and Martin Roth (1955). These provided evidence that not all mental disorders could be ascribed to senility and opened the possibility of offering effective treatments for certain disorders, especially affective states. Services dedicated to older people began to open in a patchy fashion across the UK (e.g. Arie, 1970). The common interests of psychiatrists working in this area led first to the formation of an informal gathering, followed by an official Group within the Royal College of

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Psychiatrists in 1973, and then a full Specialist Section in 1978. Old age psychiatry was recognized by the UK Department of Health as a separate specialty in 1989 (Hilton, 2016). Numbers of consultant old age psychiatrist posts have continued to rise, the most recent estimate for England being almost 700 (Royal College of Psychiatrists, 2017a), though 12% of these were unfilled at the point of census.

For several years, the development of old age psychiatry proceeded apart from that of geriatric medicine, despite the obvious overlap in clientele. The reasons for this were complex, often including personal factors and differing expectations and cultures (Hilton, 2014). More common ground was reached by a joint Royal Colleges document on the care of older people with mental illness (Royal College of Psychiatrists/Royal College of Physicians, 1998). Neurology was a relatively late entrant into the field as for many years British neurology paid little attention to cognitive disorders. This has changed dramatically since the 1980s and advances in brain imaging and neuropsychology. Policy also lagged behind the developing clinical services, and until the publication of *Services for Mental Illness Related to Old Age* (Department of Health and Social Security, 1972), there had been no conceptual progress for over 20 years (Hilton, 2005a).

Developments in other countries have been influenced to varying degrees by the UK experience. Patterns of service reflect national factors such as the nature of the healthcare system, the degree to which old age psychiatrists are generalists or dementia specialists, and the level of resources in the individual country. Snowden and Arie (2005) described service developments and also the establishment of national and international organizations for old age psychiatry. Founded in 1982, the International Psychogeriatric Association (IPA) has been particularly influential. The World Psychiatric Association (WPA) (Camus et al., 2003) found that 40 out of 48 countries responding provided some specific mental health services for older people, and 13 of these countries recognized old age psychiatry as a separate specialty.

Principles and values

One of the strengths of old age psychiatry, besides its consideration of epidemiological factors, has been a keen interest in the values underlying its practice. For example, Arie and Jolley (1982) identified five principles: flexibility; responsiveness and availability; unhierarchical use of staff; domiciliary assessment; and willingness to collaborate with other services and agencies. This list has been amended in various places, but the most general statements of values are to be found in series of consensus statements, jointly issued by the World Health Organization (WHO) and the Geriatric Psychiatry Section of the WPA.

These bodies produced five consensus statements concerning: psychiatry of older people; organization of care; education (these three subsequently compiled as a single statement; WHO, 1999); reducing stigma and

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discrimination against older people with mental disorders (WHO, 2002); and ethical practice (Katona et al., 2009). Of these, the consensus statement focused on organization of services has probably been most influential and it is the most relevant to this chapter. As well as setting out seven underlying principles (forming the acronym CARITAS; Comprehensive, Accessible, Responsive, Individualized, Transdisciplinary, Accountable, and Systemic), the document describes the various types of care that may be provided and the components of specialist services. The consensus statement on ethical practice (Katona et al., 2009) discusses the needs for the application of high ethical standards in clinical practice, especially in relation to mental capacity and decision-making.

Values in relation to dementia were set out by the National Dementia Declaration for England, produced by the Dementia Action Alliance, a partnership with 41 signatories representing government, professional bodies, and voluntary and independent sector organizations. The Declaration set out a set of desired outcomes for people with dementia, which have now been updated and expanded as a set of Dementia Statements (Dementia Action Alliance, 2017; see Chapter 15 for a fuller account). The main focus is on people with dementia, to enable them to make their own choices and decisions wherever possible, though it also acknowledges carers as equal partners. The Statements call on individuals and organizations to sign up in order to further the delivery of national dementia policy and these outcomes in particular.

Policy

United Kingdom

Space precludes a discussion of the whole policy framework of relevance to older people. Obviously, this group is particularly affected by reforms to health services and changes in social care policy and funding. In the wider economy, the current debate over pensions will affect the material prosperity of the next generations as they grow older, with people likely to continue working longer. Some more relevant issues, e.g. the roles of public bodies in regulating services and promoting best practice, are discussed later in this chapter. In England, there is no single strand of policies relating to older people's mental health. There is instead a separation between dementia, on the one hand, and other mental disorders, which are considered across the entire age range, on the other. This dates from the publication of separate National Service Frameworks (NSFs) for Mental Health (Department of Health (DH), 1999) and Older People (DH, 2001). The first covered mental health up to age 65, and the second incorporated mental health issues in older people, emphasizing dementia and depression, along with physical illnesses like stroke. Subsequently, because of concerns about possible age discrimination, mental health policy was extended across the age range.

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Mental health policy in England is currently set out in *The Five Year Forward View for Mental Health* (NHS England, 2016). It focuses on: services available seven days a week, especially crisis services; an integrated approach to physical and mental health care; mental health promotion and prevention; and looking forward, in terms of research and improved management of clinical data. As regards older people, there is a welcome emphasis on the importance of recognizing and treating depression. There is specific mention that patients in old age medical settings should have access to expertise in old age psychiatry. However, the *Five Year Forward View* is ambiguous about the separate existence of old age psychiatry: 'Older people should be able to access services that meet their needs—bespoke older adult services should be the preferred model until general adult mental health services can be shown to provide age-appropriate care.'

As regards dementia policy for England, the *National Dementia Strategy* (Department of Health, 2009) was an important step featuring 17 objectives, including improved public awareness, early diagnosis and intervention, improved quality of care in various settings, research, and implementation. This was followed by the then Prime Minister, David Cameron, taking a personal interest and issuing the *Prime Minister's Challenge on Dementia* (Department of Health, 2012). The *Challenge* had three main areas: improvements in health and care; creating dementia-friendly communities; and research. An updated version was published extending up to 2020 (DH, 2015). Among other things, the revised version placed more emphasis on the area of post-diagnostic support and made some specific commitments in relation to dementia research.

The other devolved nations of the UK—Scotland, Wales, and Northern Ireland—all have similar initiatives to those in England (see Scottish Government, 2017; Welsh Government, 2017; Department of Health, Social Services and Public Safety, 2011).

Other countries

At the time of writing, there are around 20 other European countries with a national dementia strategy, with several others in draft (Alzheimer Europe, 2017). Through its Glasgow declaration (Alzheimer Europe, 2014), Alzheimer Europe and the individual national dementia organizations have called for a Europe-wide dementia strategy, though this has not so far been forthcoming. Elsewhere in the world, Australia was probably the first country with a national dementia strategy, launched in 2005. The current version covers the period up to 2019 (Australian Government, 2015). In the US, the National Plan to Address Alzheimer's Disease was recently updated (US Department of Health and Human Services, 2017). It covers all forms of dementia, not just Alzheimer's disease and, while it is national in scope, it is not Federal, so initiatives are quite variable across regions. At the time of writing the newest national dementia plan was that of Chile (November 2017).

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As would be expected, given the scale of dementia worldwide, there have been several international initiatives in recent years. These include several excellent and influential annual reports on different aspects of dementia (e.g. prevalence, economics) from Alzheimer's Disease International (ADI) (see <https://www.alz.co.uk/research/world-report>). The WHO and ADI jointly published *Dementia: A Public Health Priority* (ADI and WHO, 2012) as a call to action for governments. In 2013, the G8 group of nations held a summit for health ministers on the theme of dementia (see https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/265869/2901668_G8_DementiaSummitDeclaration_acc.pdf). Following this, the WHO has published a global action plan on dementia (WHO, 2017a), along with a practical set of guidance, *Integrated Care for Older People* (WHO, 2017b) for preventing and managing functional decline in later life, which makes evidence-based recommendations for simple practical measures that can impact upon health even in low-income countries (LICs).

Services in low- and middle-income countries (LMICs)

There are gross disparities in resources and funding for healthcare between and within developed and developing countries. LICs lack the economic and human capital to contemplate the widespread introduction of specialist services. Instead, the focus must be on developing primary medical care services (Snowdon, 2007). Long-term care facilities are also rare in developing countries where traditional family care arrangements continue to be the main focus of care. Older people tend to live in multigenerational households and families are the main caregivers for relatives with dementia. This is certainly the case in the two most populous countries of the world, China and India (Shaji et al., 2002). Within individual countries there are often also inequities between the services available to rich and poor people, as well as between urban and rural dwellers. The affluent often have access to excellent specialist centres but this is not the case for the masses. Services in disadvantaged areas are often limited to acute care with little in the way of ongoing support or care in the community.

As resources will always be a challenge in low- and middle-income countries (LMICs), integrated psychogeriatric models should be encouraged rather than specialist services. This would mean integrating psychogeriatric services with other mental health services including outreach services in primary care settings (Wang et al., 2013). Services need to have realistic goals, they should be based on careful mapping of all local resources that may be supportive of older people, and they can work through general health workers with suitable brief training (Denning and Shaji, 2005).

This requires improvement of education and training for medical students and general practitioners about mental health of older persons. One approach in China has been to train nominated dementia doctors as

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physicians to support primary care (Chen, L.K., et al., 2014). Dementia support doctors facilitate multidisciplinary cooperation and give lectures about dementia to primary care physicians and educate people in the community. Through these approaches they were able to increase the numbers of medical and care professionals specializing in dementia and to establish systems to provide them necessary education.

Recognizing and treating common mental disorders in old age should be part of the training curriculum of all health personnel in LMICs. This has been done to a limited degree but not nationally in countries like China, India, and some South East Asian countries. There is a need to develop locally relevant and adapted training materials. Again, this has been undertaken with some success in a few LMICs. There are examples of excellent work in this area.

The WHO South East Asia Regional Office published a list of minimum actions for individual nations to take in response to the mental health needs of their older populations (de Mendonça Lima et al., 2010) (see Box 20.1). Services in LMICs are discussed further in Chapter 21.

Box 20.1 Actions for mental healthcare for older persons

- 1** Mental health (MH) problems for older people are managed within primary care.
- 2** Ensure availability of essential psychotropic drugs to old persons.
- 3** MH care for older people is delivered in the community by personnel specifically trained and working in adapted structures. MH care services should promote mental health and the early identification of MH problems in old age. Avoid the use of inappropriate institutional settings. A specialist old age psychiatry service should be available for at least advice and some referrals.
- 4** Educate the public and support non-governmental organizations in public education on specific topics concerning old people.
- 5** Involve communities, families, and consumers, e.g. promote the formation of self-help groups to support individual patients, together with families and caregivers. Such initiatives require funding.
- 6** Ensure that the MH programmes, policies, and budgets sufficiently take into account the needs of old people.
- 7** Train primary health care workers in psychiatry of older persons and ensure that psychiatry of old age is taught in graduate and postgraduate courses dealing with health care of older persons.

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- 8 Develop programs to prepare people for retirement and develop support for non-governmental organizations working in this area.
- 9 Monitor community MH of older persons by including mental disorders in older persons in basic health information systems and by conducting local and national surveys.
- 10 Support research about prevalence, course, outcome and impact of mental disorders in old people living in LMICs.

Source: data from De Mendonça Lima C, Leibing A, Buschfort R. (2010). Ageing and mental health resources for older persons in the WHO South East Asia Region. *Psychogeriatrics Polska*, 7(3), 83–90.

The nature and scope of old age psychiatry services

This chapter is mainly concerned with specialist services for older people with mental health problems. The boundaries of this activity are rather imprecise, and most interactions with older people and mental disorders will be in social care settings, such as day centres and home care services, or in primary care, where most common disorders, such as depression, frequently present. The contributions of primary care and social care are discussed in Chapter 22 and Chapter 25, respectively. Another important point of contact is in general hospitals (see Chapter 24, which discusses liaison psychiatry for older people).

There are also variations as to the boundaries of specialist services. In some countries, especially if old age psychiatry is not a recognized specialty, this work may be undertaken by general psychiatrists, geriatric physicians, or neurologists. For example, in the US, dementia is largely regarded as a neurological disorder, so that most diagnostic work is undertaken by neurologists, and dementia research lies within the remit of the National Institute of Neurological Disorders and Stroke. Where designated old age mental health services do exist, some limit themselves to dementia, while others accept a full range of mental health conditions. Some services operate as 'all-age' teams for all patients over the age of 18, but have some practitioners within the team who specialize in seeing older patients—in effect operating as an old-age team within a generic service.

The term used for the specialty can also vary. In the UK, 'psychogeriatrics' has largely been superseded by 'old age psychiatry', as its practitioners have emphasized their links with the rest of psychiatry, rather than with geriatric physicians (though there is still debate about the best term to cover this field). In the US, the relevant specialty is 'geriatric psychiatry', though this is often a rather different activity from UK old age psychiatry, as the integral links with community teams are not always present to the same degree, and the diagnosis and medical

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treatment of dementia is more the concern of neurologists. Geriatric psychiatry in the US has been criticized for moving away from the principles of comprehensive, interdisciplinary assessment and therapy, and tending to abandon frail, very old people in favour of those nearer 65 with less-complex needs (Blazer, 2000).

However, despite these problems of terms and boundaries, the following section is mainly about the model of old age psychiatry that has developed from these various influences. There are two accounts to consider: one is the 'traditional' model of old age psychiatry, with its constituent components, and the other includes more recent developments that move away from this simpler model to a more diverse array of services (see Box 20.2). And, given the challenges confronting specialist old age psychiatry services, it is important to consider the evidence whether specific, age-based services provide benefits for patients and families. Draper and Low (2004) summarized a series of systematic reviews of different aspects of services and found good evidence to support multidisciplinary community mental health services, collaborative treatment of depression, and outreach to care homes. However, more up-to-date assessment of the evidence appears to be lacking.

Box 20.2 Components of old age psychiatry services

'Traditional' elements

- Community mental health teams
- Memory assessment services and memory clinics
- Day hospitals
- Respite care
- Support to carers
- In-patient care
- Consultation-liaison psychiatry
- Working with other agencies

Newer topics

- Age-inclusive services
- Primary care mental health services
- Post-diagnostic support
- Integrated care and case management
- Crisis resolution and home treatment
- Outreach to care homes

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Components of old age psychiatry services

Community mental health teams

The English National Service Framework for Older People (DH, 2001a) described a service model for community mental health teams (CMHTs) that reflected agreed norms at that time. Developments since then have been described in a series of studies by Challis and his group in Manchester that trace the changing size and practices of CMHTs (e.g. Tucker et al., 2015; Wilberforce et al., 2015; Verbeek et al., 2018). The core members of the specialist mental health service include consultant old age psychiatrists, community mental health nurses, clinical psychologists, occupational therapists, and social workers. Additional untrained staff, such as health and social care assistants, often make significant contributions (Wilberforce et al., 2017), and adequate administrative support is essential. Agreed working and referral arrangements with other professionals, such as speech and language therapists, physiotherapists, and dieticians, are also required, though these disciplines are not usually members of the team itself. Most CMHTs have this structure, although variations are often seen in practice. Most frequently, one or more professional groups may be lacking—often clinical psychology as there is a lack of practitioners working with older people. There may just be a single consultant psychiatrist for a team, and the consultant may work somewhat detached from the team, perhaps taking separate referrals but also having other commitments elsewhere, e.g. in-patient units.

CMHTs characteristically cover an agreed sector, which may be defined geographically or else by which general practices refer to the team. In the UK, teams usually deal with the full range of mental disorders, not solely dementia. There will be an agreed route of referral, with most referrals in practice coming from primary care, but also from other sources, including social services, residential homes, and sometimes directly from families. Patients appear reluctant to refer themselves, even to teams with open referral policies. Teams are of variable size, often smaller in rural areas. Within a larger team, there is scope for some subdivision of responsibilities or for specialization. For example, each member of the team may be linked to an individual GP surgery or have links with one or more residential or nursing homes in the patch. Or they may develop special roles, such as monitoring patients on antimental drugs.

Leadership in teams is a commonly discussed theme, but there are several aspects to how a team is led. For example, the CMHT will be managed as part of the service to which it belongs; the staff in it will be line managed; they will also have their own professional group hierarchies, which may include supervision of their clinical work; and there may be a designated team leader, whose role will include such matters as chairing the referral allocation meeting. As well as this, consultant psychiatrists provide clinical leadership to the CMHT, which seems to

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comprise a commitment to be involved in the assessment and management of more complicated cases and to act as one of the main conduits between the CMHT and other parts of the service, especially in-patient care.

There is good evidence that CMHTs for older people offer effective interventions. In one of the first evaluations of the impact of a community team, O'Connor et al. (1991) found that early intervention led to *increased* admissions to long-term care within a two-year period for people with dementia living alone. This may have reflected that this group was in fact living in conditions of high risk and relative neglect, though in a more recent study Wilberforce and colleagues (2016) also found that well-integrated CMHTs improved access for patients to other community services but did not reduce rates of institutional admission. Callahan and colleagues (2006) found that an interdisciplinary team working collaboratively with primary care provided significant improvements in the quality of care and in behavioural and psychological symptoms of dementia among primary care patients and their caregivers. Rothera and colleagues (2008) found that a multiagency specialist support team for older people with dementia achieved better outcomes than standard services. Occupational therapy interventions have also been the subject of randomized trials in Europe, with rather conflicting results despite initial promise (Graff et al., 2006; Voigt-Radloff et al., 2011).

However, most RCTs of interventions by CMHTs have concentrated on depression (Draper and Low, 2005). Of these, four out of six reported that the team input was more effective than the control intervention, and these findings have been supported by data from several uncontrolled studies.

There is a good case that assessment and management should take place at home where possible, rather than, say, in outpatient clinics. The advantages of this include being able to take in aspects of the patient's social surroundings in one visit, as well as being highly acceptable to many older people. Case management, in various forms, often known in the UK as the Care Programme Approach (CPA), is an effective way of ensuring that patients are kept in contact with the service. Case management seems to be effective at reducing overall costs and care home admissions for people with dementia living at home (Reilly et al., 2015), but the evidence is variable due to differences in study designs and outcome measures used. It is accepted that specialist teams for older people are more effective at managing depression in older people than general adult mental health teams, though this has not been formally evaluated (Draper and Low, 2005).

As regards the specific role of psychiatry, consultant home visits are probably best targeted at more complex cases requiring diagnosis and the initiation of treatment, but there are few if any recent studies of this practice. Home-based practice lessens the rate of failed appointments and also may cost less than running an outpatient clinic. However, many

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old age psychiatrists hold outpatient clinics in addition to seeing patients at home. Such clinics may be very useful for following up relatively mobile patients, often those with functional disorders, e.g. assisting with managing certain patients on lithium treatment using shared protocols with primary care (Head and Denning, 1998).

Thus, CMHTs for older people are well established in various countries, and there is good evidence to support this style of service. There remain several issues where further research evidence would be helpful. For example, there are no studies that evaluate patient outcomes from specific members of the multidisciplinary team.

Memory assessment services and memory clinics

These specific topics are discussed in Chapter 23. As mentioned earlier in The nature and scope of old age psychiatry services, in many countries patients referred for memory assessment are seen by geriatricians or neurologists, with the role of the psychiatrist being much more to deal with behavioural and psychological problems in people who already have a diagnosis. The English National Dementia Strategy (DH, 2009) placed much emphasis on the importance of early diagnosis and called for the development of new memory assessment services, though it did not specify where these should be located or who should run them. However, in the UK, most memory assessments are performed by old age mental health teams. In recent years, reflecting the increasing numbers of referrals, these have often become nurse-led, with trained nurses undertaking standardized assessments under a variable degree of medical oversight. Nurse-led, as opposed to consultant-led, clinics may attract a lower proportion of referrals with MCI and dementia, especially if they have a self-referral policy (Minstrell et al., 2015).

Memory *clinics* are often, though not necessarily, hospital-based. They were first established in the late 1980s and early 1990s, often by geriatricians and neurologists as well as psychiatrists. They became more widespread and increasingly the domain of old age psychiatry (Lindesay et al., 2002). They are an efficient vehicle for diagnostic assessment and investigation of possible dementia and mild cognitive impairment, and were often set up for research purposes such as recruiting patients to trials of antidementia drugs. However, memory clinics can face some challenging issues, such as waiting lists caused by the complex protocols of some clinics, an overemphasis on medication, and a lack of integration with social care and other community support. From the patient's perspective, the process is often labyrinthine, slow, and confusing (Samsi et al., 2014), so clearly more attention to the patient and carer view is needed when designing services. Following patients up in memory clinics appears no more beneficial than follow-up in primary care (Meeuwssen et al., 2012). Nonetheless, memory clinics can be an effective means of recruiting and monitoring patients in trials of new drugs.

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Thus, memory clinics have tended to broaden their scope, focusing less on academic research and more on early cognitive problems (Ramakers and Verhey, 2011). However, the emphasis is now more on memory *services*, which can be more population based, providing assessments and interventions closer to home. Various models exist, e.g. services based around assessment at home (Banerjee et al., 2007) or in primary care (Greening et al., 2009; Lee et al., 2010), as these seem to achieve high acceptability, high appropriate referral rates, and user satisfaction.

Day hospitals

Day hospitals (often referred to in the US as partial hospitalization programmes) have tended to decline over the last decade or so. Historically they were regarded as a key component of old age psychiatry services (Audini et al., 2001), though their efficacy was often questioned (Fasey, 1994). Day hospitals for older people with medical illnesses offer benefits compared with no treatment, but they are not more effective than alternatives such as home care, and therefore there is no evidence that they are cost effective (Brown et al., 2015). The same is likely to apply to mental health day hospitals for older people.

In the UK, day hospitals are generally distinguished from day centres, the latter being run by social care providers and the voluntary sector, whereas day hospitals are part of the health service. There are therefore differences in funding and staffing arrangements in each type of facility. Day hospitals are more likely to focus on assessment and therapeutic activities (Reilly et al., 2006), and are generally looking to discharge patients elsewhere, either after an agreed period of attendance or once a suitable outcome has been achieved. Day centres do not have the same emphasis on assessment, activities are generally diversionary rather than therapeutic, and indefinite attendance is not usually a problem.

Wilson and Hussain (2008) provided a review of the changing status of day hospitals, which included standards for auditing service quality. Virtually no research has been published since then, which reflects the continuing decline of day hospitals. Many have closed completely, often as a cost-reduction exercise, or else their functions are limited to specific, short-term activities, e.g. post-diagnostic support or the provision of cognitive stimulation therapy.

Respite care

Respite can be regarded as a service (that provides carers with a physical break from their responsibilities) or as an outcome (a psychological break) (O'Shea et al., 2019). It has the limitation that it focuses upon the carer's side of the relationship, with the interests and wishes of the person who has dementia being relatively neglected. O'Shea and colleagues therefore suggest that 'restorative care' would be a more helpful term to employ.

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That having been said, respite care comprises a mixture of activities aimed at giving caregivers temporary opportunities to be away from the patient in order to reduce their stress and to delay or prevent care home or hospital admission. There are broadly three types of respite: short residential placements, day care, and home care. Short-stay respite care is generally provided in residential and nursing homes rather than in hospitals. Respite care may be planned, offered in a crisis, or at the request of the carer.

More recent systematic reviews of 'frail older people' (a category that includes many people with dementia as well as physical health problems) (Mason et al., 2007; Shaw et al., 2009) found evidence of some benefit to carers in terms of decreased burden and improved mental and physical health. There was no reliable evidence that respite either benefits or adversely affects the care recipient, or that it delays entry into residential care. Evidence around respite care for dementia is patchy (Maayan et al., 2014; Vandepitte et al., 2016) but suggests that day care helps caregiver burden; conversely temporary residential admission may cause disruption for both the carer and the person with dementia (PWD); and home-based community respite shows promise but has not been well evaluated. A review of the effects of residential respite care on the behaviour of older people with dementia found variable results, with a modest but short-term reduction in symptoms in some studies (Neville and Byrne, 2007).

However, in practice, many carers regard respite as a priority, especially if it is flexible and readily available (Kampanellou et al., 2017). Carers of people with dementia are more likely to use respite care than carers involved with other long-term conditions (Vecchio et al., 2016) and they often describe high levels of satisfaction with it. When respite care is not used, this seems to be mainly caused by carers' beliefs about adverse outcomes (Phillipson et al., 2013). Respite care may be used by some carers to help them keep the PWD at home for longer, whereas, for others, respite care functions as a stepping stone on the way to long-term care, so it is not surprising that there is no demonstrable effect in delaying admission into residential care. Sometimes, perhaps, respite care is offered when what is really needed is long-term care, in which situation it may be regarded as a form of rationing. Overall, it does appear that providing respite in various forms, in partnership with other agencies, is a legitimate activity for old age psychiatry services.

Support to carers

Old age psychiatry was perhaps one of the first areas where carer issues were first recognized (e.g. Argyle et al., 1985); Chapter 54 provides a more detailed account of this topic. In summary, countless papers have documented how carers of people with dementia seem to have particularly high levels of stress and physical ill health (Gilhooly et al., 2016), together with lower levels of satisfaction with services than other carers. However, the problems of caregiving can be overstated in clinical samples, and a more balanced view is probably more appropriate. Positive

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aspects of caregiving can include a sense of personal accomplishment and gratification, feelings of mutuality in a dyadic relationship, an increase of family cohesion and functionality, and a sense of personal growth and purpose in life (Yu et al., 2017). It is also clear that the previous quality of the relationship with the affected person is an important influence on the experience of caregiving (Quinn et al., 2009).

As a consequence of the importance of carers and their relationship with the PWD, assessments of patients also routinely include assessment of the carers' mental state and coping resources. Indeed, in the UK, carers are legally entitled to their own separate assessments. A carer's needs appear to have two components (McCabe et al., 2016), the first being in relation to the PWD and their care (information about the condition, behaviour changes, access to care) and the second being the carer's own needs (which includes their own health but also their sense of having a life).

Most services provided for patients will also directly or indirectly benefit carers: for instance, treating the patient's symptoms can make life more tolerable for the carer. Many of the services for people with dementia, e.g. day care, respite care, and the management of difficult behaviour, are often aimed primarily at improving matters for the carer. Several systematic reviews have shown that psychosocial interventions for carers of people with dementia can be effective across a range of outcomes (e.g. Selwood et al., 2007; Gilhooly et al., 2016). Perhaps sadly, befriending interventions for carers do not seem to be effective, due mainly to low rates of uptake (Charlesworth et al., 2008).

As well as this, there is considerable interest in supporting carers (especially carers of people with dementia) through educational and other means. At the most basic level, this includes carer support groups, where carers can provide mutual support by sharing experiences and passing on skills they have learned from their own roles. More formal programmes have been developed and evaluated that comprise various elements, such as improving carers' knowledge of mental health problems and teaching exercises to deal more effectively with challenging behaviours; early examples include Mittelman et al. (1996) and Brodaty et al. (1997). The best evidence is for teaching behaviour management strategies in response to the PWD's behaviour, with individual sessions appearing more effective than group interventions (Selwood et al., 2007).

One particular model of working with carers is that of Admiral Nurses. These are specialist mental health nurses working in the field of dementia. The emphasis in their work is on working with family carers, as well as with the PWD. The concept of Admiral Nurses belongs to the charity Dementia UK (<http://www.dementiauk.org/>), which was founded to respond to the unmet needs of family carers. It is a popular model with carers and families as the nurse remains in contact with them throughout the patient's journey. There is a challenge for the model to demonstrate improved outcomes beyond service evaluations and individual case studies (Knight and Denning, 2017), but, more pressingly, as the nurses

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are often funded on a start-up basis, they are vulnerable to cost-saving measures in local services.

Carers also have an important role to play in the formal and informal education of personnel training in old age psychiatry and other professional groups; they can provide a valuable independent perspective in the evaluation of mental health services (Denning and Lawton, 1998). They are often the most passionate and effective lobbyists especially on behalf of people with dementia. Carers are an important force in organizations such as the Alzheimer's Society in England and equivalent organizations elsewhere. They often form the core of public and patient involvement in dementia research and can have an important part to play in setting the research agenda (Kelly et al., 2015).

In-patient care

Across the world, there are varying patterns of in-patient provision for older people. In LMICs, there are often relatively few in-patient mental health beds generally, so in-patient care is a less important contributor to the overall picture. Some countries, notably in eastern Europe, still have large mental hospital populations, in which there may be no specific provision for older people. Elsewhere, there has been a considerable fall in mental health bed numbers as large old-style hospitals have been closed down. In England, for example, mental health bed numbers have fallen from 67,000 to 18,407 in the last 30 years (NHS England, 2019), with no sign of this trend having finished. In other countries, e.g. Australia, bed numbers have been stable in the last few years. For most countries, it is difficult to obtain accurate figures for older people's mental health beds, even if specific provision exists.

There are some significant issues around mental health in-patient care for older people. Wards for older patients are usually separate from those for adults under 65. Wards for mixed ages tend to disadvantage older people, who may be relatively neglected in the face of demands placed by younger, psychotic, and disturbed patients. It is also customary to separate dementia and functional illness, since experience suggests that depressed patients find the presence of patients with dementia and behaviour problems quite difficult to bear. In-patient care for dementia largely caters for patients with particularly difficult behaviour problems. In general, hospitals do not provide long-stay care for people with dementia and, in the UK and elsewhere, this care is usually provided by residential and nursing homes (see Chapter 26).

Published evidence indicates that good links between in-patient units and their respective community teams are beneficial for patients. In the past, it was usual for a consultant psychiatrist to be responsible both for in-patient beds and the corresponding sector of the community, but this is now less common and it is more usual to have a separation between in-patient and community consultants. This can lead to problems in communication and discontinuity of care unless liaison between the

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teams is given suitable priority. Community follow-up, including outpatient attendance and community psychiatric nurse visits, reduces readmission for patients with depression. Longer lengths of stay in hospital are also associated with fewer readmissions, but the relationship between length of stay and other outcomes is less clear. Studies of in-patient treatment suggest quite good treatment outcomes, both for depression and for behavioural and psychological symptoms in dementia (BPSD) (Draper and Low, 2004).

Although joint assessment wards with geriatric medicine were at one time recommended, they are now uncommon. A recent trial of a specialist medical and mental health unit achieved improved patient experience and carer satisfaction but no significant improvements in health outcomes, probably because the patients were very elderly and many were close to the end of their lives (Goldberg et al., 2013). Various factors have contributed to the decline of joint units, but it appears that geriatric physicians are more comfortable with a responsive psychiatric liaison service, and geriatric psychiatrists are satisfied if there is adequate access to medical and diagnostic facilities for their physically unwell patients. It is sometimes somewhat arbitrary as to the bed in which a person is finally placed. Evidence suggests that older patients with dementia in acute hospitals have worse outcomes (Sampson et al., 2009) and patients with depression fare better in mental health care than in general wards (Norquist et al., 1995).

Consultation-liaison psychiatry

Older people in acute hospitals have high levels of psychiatric morbidity, especially dementia and depression. Referrals of patients in general hospital beds generate high volumes of work for old age psychiatry services. This important topic is discussed in Chapter 24. From the point of view of this section, it is worth noting recent developments in this area.

Consultant psychiatrists have always had an important role in diagnosis and advice about treatment in medically complex situations, but in isolation cannot hope to deal with the volume of mental health needs in a large general hospital. In the UK, the report *Who Cares Wins* (Royal College of Psychiatrists, 2005) set out clear recommendations for improved liaison services. Tadros and colleagues (2013) developed the RAID (Rapid Assessment, Interface and Discharge) service and showed that, by reducing lengths of stay in hospital, it could reduce the needs for beds by about 10% with concomitant financial savings. Although RAID was not specifically aimed at older people, most of the impact was upon beds occupied by older people. This model has attracted wide interest and investment in liaison services in the UK.

Relationships to other agencies

There are several key relationships to consider, several of which are discussed in more detail in other chapters of this book. They include working with primary care (Chapter 22), other branches of medicine

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(Chapter 24), social services (Chapter 25), non-government agencies, and residential and nursing homes (Chapter 19 and Chapter 26). End-of-life care, especially in relation to people with dementia, has become an increasingly important area of research and practice in recent years. Palliative care and end-of-life issues involve all of these different agencies (see Chapter 27 and also Chapter 53 for end-of-life issues in dementia).

Age-inclusive services

There is justifiable concern that people should not be discriminated against on the basis of their age. Indeed, age discrimination has now become illegal in the UK through the Equality Act 2010. Part of the reason for this legislation was evidence that older people were denied access to certain health services solely on the grounds of their age (Lievesley, 2009). For example, in the field of mental health, this often included access to psychological treatments. How age equality should be translated into mental health services remains a matter of debate. The two opposing viewpoints are, on the one hand, that age inclusiveness means that a separate specialist service for older people is in itself discriminatory, and, on the other, that the needs of older people are distinct and therefore age equality does not mean scrapping the older people's mental health services as a separate entity.

The authors' view is that the second viewpoint is correct. In some parts of the country, services for older people have indeed been merged with those for younger adults. There may or may not remain a separate service for the assessment and management of dementia. This has been as much a cost saving measure as for the clinical benefit of patients. However, in such general services, it is always likely that the more immediate physical risks posed by younger patients, especially those with psychosis, substance misuse problems, and personality disorders (often in combination), will take up much of the attention of the team to the detriment of older people (Warner and Jenkinson, 2013). Mixed age, 'age-inclusive', in-patient units are often characterized by depressed older people cowering in corners and being generally neglected. Even within community teams, it is difficult to maintain the specific expertise required for supporting older people.

Of course, in present times, most people in their late sixties do not regard themselves as old, especially if they have good physical health and either employment or a viable pension. There may be a case for a more flexible boundary between younger adult services and older people's services, based on need rather than exact chronological age. However, beyond this stage in life, cognitive impairment and/or physical ill health become much more important features, and so the approach to assessment and diagnosis is very different for someone in their eighties or nineties to that for a 30-year-old. There are special skills in either case and it is important that these are maintained and not lost in the pursuit of political correctness. Box 20.3 shows the current criteria for old age psychiatry services developed by the Faculty of the Psychiatry of Old Age (Royal

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College of Psychiatrists, 2015) and the Royal Australian and New Zealand College of Psychiatrists (2015).

Box 20.3 Current criteria for old age psychiatry services

Royal College of Psychiatrists (2015)

- 1 People of any age with a primary dementia.
- 2 People with mental disorder and physical illness or frailty that contributes to, or complicates, the management of their mental illness. This may include people under 65 years of age.
- 3 People with psychological or social difficulties related to the ageing process, or end-of-life issues, or who feel their needs may be best met by a service for older people. This would normally include people over 70 years of age.

Royal Australian and New Zealand College of Psychiatrists (2015)

- 1 People with serious mental disorder, aged 65 or older, newly presenting to local mental health services or who have not been under the care of other local mental health services for a regionally-specified amount of years.
- 2 People with serious mental disorder and significant age-related physical illness or frailty which compounds or complicates the management of the mental disorder.
- 3 People with serious mental disorder and significant psychological or social difficulties related to the ageing process where their needs may best be met by a service for older people.
- 4 People of any age with a primary dementia and serious behavioural and/or psychological symptoms.

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An argument is sometimes presented that services for 'functional' disorders can be provided separately from dementia, and therefore that the functional part of the service can safely be amalgamated with the general adult service. However, this overlooks one of the central diagnostic challenges for old age psychiatry, which is the assessment of states (such as mild cognitive impairment, late onset depression, and depression with a physical illness) where it is not clear whether or not the problem is mainly organic and, if so, to what extent. Many of these cases cannot be easily assigned to 'functional' or 'organic' categories.

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There are numerous challenges to achieving equality in mental health services (National Development Team for Inclusion, 2011). These include such issues as a lack of data on outcomes for older people; poor experience of services, notably in general hospitals; inequity of access to treatments and other services; and low expectations and pessimistic assumptions about outcomes for older people. To bring about improvements requires leadership and a clear vision as to what truly constitutes age equality, making more use of the voices of service users and carers, as well as demonstrating the use of evidence-based practice.

In summary, it matters not so much how the services are organized as that there is a clear philosophy and a genuine commitment to equality of access to appropriate support irrespective of age. However, this does require recognition that older people's issues are different in certain ways and therefore specialist expertise is relevant and necessary. There is a real risk that in 'age-inclusive services', older people may be neglected because of the pressures generated by younger patients, and the leadership of such teams may not have the necessary expertise and understanding of older people's issues.

Primary care mental health services

Most consultations related to mental health take place in primary care and most patients are not, and do not require to be, referred to specialist mental health services. In recent years, there has been much more interest in the actual services that might be offered to people attending primary care, apart from seeing a GP or the practice counsellor. A primary care setting may have advantages over being seen by a specialist mental health team, e.g. familiarity, convenience, a broader focus on physical health matters, availability of blood tests, and prescribing. Primary care mental health is seen as having two components: first-line interventions that are an integral part of general health care; and mental health care, which is provided by primary care professionals who are skilled, able, and supported to provide it (Funk and Ivbijaro, 2008). The latter group may include primary care mental health workers, a relatively new professional group, who in practice are often graduates looking to gain further experience before entering a clinical profession. They tend to work on a generic basis, though obviously some patients will be elderly. It should be noted that educational interventions to improve GPs' diagnostic and management skills in dementia are usually unsuccessful (Iliffe et al., 2015).

In addition, other workers from older people's specialist mental health teams may be based in primary care, for example, community psychiatric nurses, but generally they have remained part of a CMHT in order to prevent professional isolation. In some places, as mentioned earlier, memory clinics may be based in a primary care setting.

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Another important development in the UK has been the programme Improving Access to Psychological Treatments (IAPT) (<<http://www.iapt.nhs.uk/>>), which was established in 2006 and extended to older adults in 2010. IAPT provides cognitive behaviour therapy at two levels of intensity. There is a standard approach, and routine outcome measurement forms part of the package. Although IAPT is not technically a primary care mental health service, as referral is usually required, it sits closer to primary care than traditional mental health services, and clinics are often held in primary care or close at hand. It remains questionable whether older people in fact receive fair access to the service—but when they do, they have outcomes at least as good as younger people (Prina et al., 2014).

Finally, collaboration between primary care and specialist mental health services is clearly important, covering all aspects of the patient's journey from referral to admission, follow-up, and back to primary care. Several important studies from the US have demonstrated the advantages of collaborative care between specialist services and primary care for older people, both those with depression (Unützer et al., 2002; Von Korff et al., 2011) and those with dementia (Callahan et al., 2006, 2011). What is not yet evaluated is whether such collaborative arrangements will confer similar benefits in other health systems with more of a tradition of community-oriented old age psychiatry, and thus trials in other countries are needed.

Post-diagnostic support

Until fairly recently, there has perhaps been more emphasis placed on getting a diagnosis of dementia—referral pathways, diagnostic assessment, the impact of a diagnosis. The recent drive in countries such as the UK to increase the proportion of people with dementia receiving a diagnosis has highlighted the question as to what happens then. Alongside this, resources to CMHTs for older people, who traditionally undertook this role, have been reduced in recent years. The expectation is that patients with dementia, once diagnosed and, if appropriate, commenced on treatment should be discharged from specialist care rather than maintaining indefinite contact with the mental health service. In consequence, there is the prospect of increasing numbers of people being diagnosed with dementia but with little being offered to them.

In response, attention has been placed on the rather nebulous concept of post-diagnostic support. Everyone agrees that it is a good thing and that people should have access to it: see, for example, the Department of Health (2016) joint declaration. However, issues of important detail, such as who will provide it and where the resources will come from, are generally missing from such statements. The Scottish Government (2017) has made most progress in defining and operationalizing post-diagnostic support based on two models from Alzheimer Scotland. These are the Five Pillars for post-diagnostic support (Simmons, 2011) and the Eight Pillars for integrated care co-ordination in moderate to severe dementia

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(Kinnaird, 2012). The components of these two models are listed in Box 20.4. The Scottish Dementia Strategy (Scottish Government, 2017) includes a commitment to a guaranteed minimum of one year's post-diagnostic support, which will be continued for the duration of the person's time living with dementia or until their needs change and they require a greater degree of care coordination. It remains to be seen whether this promise can be met, in terms of the available resources and also whether the assigned link workers will have the ability to access the necessary services (Moir and Miller, 2015). Such general services are usually based around a model of Alzheimer's disease and may be less appropriate for the needs of people with other types of dementia.

Box 20.4 Alzheimer Scotland Pillars of post-diagnostic support

Five Pillars: To support people after diagnosis

- 1 Help to understand the illness and manage its symptoms
- 2 Support to stay connected to the community
- 3 Peer support from other people with dementia and their families and carers
- 4 Help to plan for future decision-making
- 5 Support to plan the shape of the person's future care from their own perspective

Eight Pillars: Community support for living at home

- 1 Dementia Practice Coordinator
- 2 Therapeutic interventions to tackle symptoms of the illness
- 3 General health care and treatment
- 4 Mental health care and treatment
- 5 Personalized support
- 6 Support for carers
- 7 Environment
- 8 Community connections

Source: data from Simmons, H. (2011). Getting Post Diagnostic Support (PDS) right for people with dementia; Adapted from Kinnaird L. (2012). Delivering Integrated Dementia Care: The 8 Pillars model of community support. Alzheimer Scotland, Edinburgh.

Hopefully, any major initiatives in post-diagnostic support will be supported by research into how effective and cost-effective they are. One relevant study, a randomized controlled trial of an eight-week manualized intervention aimed at supporting the mental health of family carers (Livingston et al., 2014), showed clinical and cost-effectiveness and merits further work on its implementation (Lord et al., 2017).

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Despite any shortcomings of what is currently on offer, it is clear that giving people a diagnosis of dementia is not an end in itself, and it is what happens subsequently that makes a real difference to their lives and those of their families. PWDs and their families place great value upon having access to professionals with dementia expertise, potentially over an extended period. Currently this is often frustrated by organizational boundaries and funding issues. It should be more of a priority.

Integrated care and care management

Mental disorders in later life are complex, as they may extend over several years, frequently co-exist alongside physical health problems, and may require input at different times from a range of different practitioners and agencies. Therefore, attention is needed to specify what input may be regarded at what stage and also how the various inputs will be coordinated, otherwise people will not receive the help that they need at the appropriate time, and there may be neglect or unnecessary duplication of effort. Most of the work in this area has been done around dementia, so the rest of this section focuses on dementia, but similar issues apply to the management of other conditions, such as depression and enduring mental illness.

Integrated care pathways (ICPs) are a means of describing the patient's journey with the condition in question, and numerous examples are available for dementia, for example, that provided by NICE (2018b), which is an interactive flowchart displaying an overview pathway with subsidiary pathways for assessment and diagnosis and for management. Although such care pathways appear straightforward, there are many competing terms and definitions. For example, 'critical pathway' is the preferred term in the US and is used as the MeSH heading in the PubMed database; and De Bleser and colleagues (2006) identified 84 different definitions of the concept in the published literature. It is worth noting that using 'integrated' to describe 'care pathway' is a tautology, as a care pathway inevitably requires inputs to be integrated. Schrijvers and colleagues (2012) discussed the advantages and disadvantages of using care pathways. In short, the system is more predictable at the cost of professional autonomy and role satisfaction. A care pathway also enables components of the system to be specified and priced as part of contracts—something that has become increasingly important in modern health care.

As regards pathways for dementia in particular, the problem of ambiguity remains. Samsi and Manthorpe (2014) identified at least four applications of the term: as a means of reducing uncertainty for the PWD and for professionals; to sequence care activities; a guide to consumers; and as a manual for 'walking with' the person. Care pathways may be relevant at various stages of dementia, ranging from the identification of early symptoms to end-of-life care.

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How the pathway is implemented requires some oversight and coordinating activity. For the individual user of the pathway, this is known as care management. Again, this is a deceptively simple concept, but it has several synonyms (care management, care coordination) and numerous definitions (e.g. Lukersmith and colleagues (2016) identified 22 definitions and five competing models of case management). The sheer quantity of terms and models makes reading the relevant literature quite a challenge! Clinical trials of case management in dementia have had variable results, at least partly due to differences in study design and sampling of participants, though there is evidence of benefit for some outcomes in the medium term (Reilly et al., 2015). A Dutch study found that case management was cost effective even if there was no significant difference in clinical outcomes (MacNeil Vroomen et al., 2016). Another study examined primary care-based care managers but was unable to recruit a viable number of patients (Iliffe et al., 2014). In this case, a process evaluation suggested several contextual barriers to success, with the care managers often isolated and unsupported in their roles (Bamford et al., 2014). Successful case management needs to give adequate consideration to the role of the case manager but also to the theoretical and practical framework within which they will operate (for an example from nursing, see: Denning et al., 2017).

Crisis resolution and home treatment

Krisis (κρίσις) is a Greek word that originally meant a decision or a judgment. In English, it may refer to a difficult or dangerous time; a moment at which a decision has to be made; or a point in an illness when the outcome may turn either way, towards recovery or to death (<https://en.oxforddictionaries.com/definition/crisis>). It includes therefore the possibility of improvement or a time of opportunity, though more usually it is the negative aspects of crisis that tend to be stressed, for instance in media headlines.

Crisis theory began to be applied to psychiatry in the 1960s by Caplan and colleagues (e.g. Caplan, 1964). The first published study of a 24-hour crisis resolution team in the UK was an old age psychiatry team (Ratna, 1982), which reported a reduction in hospital admissions and increased proportion of patients remaining at home at follow-up, though it should be borne in mind that the comparison group was a cohort from an unrelated earlier study. During the 1990s, there was a significant expansion of crisis resolution and home treatment teams across general adult psychiatry, but less so for older people's services, and it is only the last decade that implementation has become more widespread in the older age group.

As regards dementia, a commonly used definition of crisis (MacNeil Vroomen et al., 2013) is 'a process where a stressor causes an imbalance requiring an immediate decision to be made which leads to a desired outcome and therefore a resolution of the crisis. If the crisis is not resolved, the cycle continues.' What constitutes a crisis may be seen from

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the perspective of the patient (e.g. falls, comorbid conditions, inability to live independently) or of the informal caregiver (e.g. emotional toll of worsening dementia, caregiver exhaustion or illness, or even death), or of health and social care professionals (e.g. physiological issues like hypothermia, nutrition, etc; psychological and behavioural problems; or concerns about the home environment). To date, there is no satisfactory typology of dementia crises.

In the UK, services have developed in a patchy manner with considerable variations in team composition, hours of working, extent and duration of support offered, whether they are stand-alone or part of a larger team, and whether they work to defined care pathways. This heterogeneity is reflected by the diverse titles that teams undertaking crisis work may have, e.g. Dementia and Intensive Support Team, Mental Health Service for Older People, Memory Assessment Service (MAS), Mental Health Intensive Recovery, Dementia Crisis Support Team, Dementia Rapid Response Team, and Intensive Recovery Intervention Service (Streater et al., 2017). Most commonly, the team exists as part of a CMHT, or as a separate home treatment team, or as part of a memory assessment service. A more rational and systematic approach is described in Victoria, Australia, with the development of Intensive Community Teams within the aged mental health system (George and Giri, 2011). Teams undertake a range of interventions, which may include any of the following:

- Identifying and working with supportive friends or neighbours;
- Environmental adaptations, e.g. assistive technology or equipment;
- Providing or guiding towards purposeful activity;
- Family carer education and support;
- 24-hour access to healthcare professionals;
- Care planning;
- Attention to physical health;
- Developing relevant, flexible care packages;
- Access to respite care or other forms of residential care when needed.

There are still relatively few studies of crisis teams for older people, most of which have a cohort design and use questionable comparison groups (Toot et al., 2011; Streater et al., 2017). There is a suggestion that crisis teams may reduce the need for hospitalization but confidence in this finding is limited by factors such as study design and possible publication bias. Future research is obviously required as to which models of may be most effective, though a bigger question is whether more energy should be spent on providing effective, ongoing, and supportive care that minimizes the risk of crises occurring.

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Support to care homes

Care home residents have high levels of dementia and other mental health problems, as well as physical comorbidity (Matthews and Denning, 2002; Gordon et al., 2014). Chapter 26 discusses in greater detail both how care home staff may struggle with residents who show difficult behaviour and how depression in residents may be easily overlooked. There are several studies over the last 20 years suggesting benefits from various mental health interventions, describing how mental health staff, either on an individual basis or as dedicated outreach teams, can operate (for a review, see: Thompsell, 2011). Challis and colleagues (2014) found that a small number of published studies of dementia outreach reported positive outcomes for residents with depression, but outcomes for dementia were less certain, apart from some reductions in prescribing antipsychotic drugs. However, at least anecdotally, such teams are often successful, valued by care homes and by GPs, but they are often vulnerable to funding reductions. Goodman and colleagues (2017, p. 119) found that the provision of adequate specialist dementia support was highly valued not only by care homes, but also by other health professionals in contact with residents.

In Australia, Dementia Support Australia (<https://www.dementia.com.au/>) is a federally funded initiative offering two services: the Dementia Care Behaviour Management Advisory Service (DCBMAS) and Severe Behaviour Response Teams (SBRT). These work across all settings but much of their work is with care homes and other aged care settings. In a UK-wide survey, Challis and colleagues (2014) also reported on the highly variable nature of provision specifically for care homes. Some CMHTs provided no dedicated staff time for this function, whereas some services include a specialist outreach team. Where a service was provided, the common elements were usually: working to a specific multidisciplinary service model; holding regular meetings with care home staff and/or GP; preparation of tailored resident care plans; and/or training and education of care home staff. As there is currently great emphasis on reducing hospital admissions from care homes, it is likely that care home outreach is likely to remain an important area of work for old age mental health in the foreseeable future.

Equality issues

The UK Equality Act 2010 makes it illegal to discriminate against a person on the grounds of what are referred to as protected characteristics. These include age, sex, disability, sexual orientation including gender reassignment, race, religion or belief, and marriage or civil partnership. Age has been considered above, but the other characteristics are also important, in addition to which certain other groups may also be at risk of unequal access to services.

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Gender

Women live longer than men, the ratio of women to men increasing with advanced age, though recent increases in life expectancy are slightly larger in men (Jagger et al., 2016) and women spend a higher proportion of their extra years of life in a state of dependency (Kingston et al., 2017) —in some regards men are catching up. Women are more likely to be bereaved and to live alone. Depression is more common in women at all ages. Worldwide, the prevalence of dementia is higher in women and women constitute at least two-thirds of the carers for people with dementia (Corfield, 2017). The majority of older people presenting to health and social care are women, so this area may legitimately be regarded as a feminist issue.

In contrast, older men are in a declining section of the population and may have difficulty finding male company and support in facilities like day centres. They are more likely to be supported by a co-resident carer, which greatly reduces their risk of moving into institutional care (Banerjee et al., 2003). However, suicide rates are higher among older men (see Chapter 40) and men have an increased risk of death after a diagnosis of dementia (hazard ratio 1.56 compared to women; Garcia-Ptacek et al., 2014).

Ethnicity

Just about all countries of the world have significant numbers of people from different ethnic and cultural backgrounds. Developed countries often have large numbers of people who have immigrated from elsewhere for various reasons, e.g. looking for work, to escape persecution. In general, minority ethnic groups have a younger age profile than the majority population, but, even so, significant numbers of older people may be involved. In England and Wales, for example, in 2011, there were 416,000 older people of non-White ethnic origin (4.5%) out of a total of 9.2 million over 65s (<https://www.nomisweb.co.uk/census/2011/lc2101ew>). Of these, just over half (57%) were of Asian/Asian British ethnicity and 28% were Black/African/Caribbean/Black British.

Minority ethnic groups vary greatly in their access to material and social resources. However, there are frequent instances in the literature of factors, e.g. social and economic disadvantage, limited opportunities in education and employment, poor health, poor access to formal services, which can then lead to higher rates of dementia (Mayeda et al., 2016), often occurring at younger ages, with limited access to care and support. In addition, there may be cultural attitudes towards mental illness, dementia, and formal services (general practices, hospitals, and care homes) that make people reluctant to seek help (e.g. Berwald et al., 2016). Failure to recognize dementia as an illness about which something can be done creates significant barriers to obtaining services (Mukadam et al., 2011) but, however, negative cultural assumptions can be tactfully challenged and even in situations where a family wishes to care for their

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relative at home they will often need information, emotional support and sometimes additional care input.

In a meta-synthesis of qualitative studies, Kenning and colleagues (2017) identified two groups of barriers—those arising from the inadequacies of available information and relevant services, and those due to cultural factors. These two areas helpfully suggest where attention is required in order to achieve better outcomes. Setting information about dementia and related topics in an appropriate cultural framework is an important starting point (e.g. Dyall, 2014; see also Fig. 20.1). Botsford and Denning (2015) have provided some recent examples of good practice, though it should be said that robust research showing that initiatives have led to better outcomes is currently in short supply.



Fig. 20.1

Example of information posters aimed at Aboriginal and Torres Island communities.

Reproduced courtesy of Dementia Support Australia (<https://www.dementia.com.au/>).

Sexuality

Lesbian, gay, bisexual, transgender, and other (LGBT+) older people may face significant challenges, as social attitudes towards same-sex relationships have been much less tolerant in the past. Transgender individuals face uncertainty given that it is relatively recent for there to be significant numbers of people who have undergone gender reassignment (Witten, 2014). Gay and lesbian partners are not necessarily recognized as the next of kin by statutory services and this

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may cause considerable distress, though the recognition of civil partnerships and marriage in many countries will ease this situation for some. In general, LGBT+ people will have fewer children to act as potential carers, so they may be more likely to enter care homes as dementia progresses (Peel et al., 2016). Issues around discrimination or disclosure remain problematic and affect the uptake of services by LGBT+ older people and carers (Addis et al., 2009; Price, 2010).

Peel and McDaid (2015) conducted focus groups around the issues of dementia for LGBT people and identified four main themes that form a useful basis for considering how professionals and services might think about responding. These themes, which were accompanied by matching recommendations, were: personal reflections on experiences of LGBT people with dementia; the identities of LGBT people with dementia; negative experiences with health and social care professionals; and provision of LGBT appropriate support and care home services. Few older people's services are targeted towards the needs of this group and with, in some instances, smaller social networks than their heterosexual peers, LGBT+ older people may need help to access statutory services, despite their low levels of trust and confidence in these services. The LGBT+ charity Stonewall provides a guide for staff working in this area (Taylor, 2017). Sexuality in later life is further discussed in Chapter 50.

Spirituality, religion, and ageing

Religiousness and spirituality have often been ignored by many mental health professionals. This area has often been neglected in clinical practice, leaving a gap to be filled by pastoral care workers, clergy, imams, rabbis, shamans, gurus, and other religious teachers. In recent years, a growing body of work in gerontology has suggested that professionals should be more aware of how the aging process motivates many people to wrestle with questions about life's meaning and purpose, including religious and spiritual experiences (e.g. McFadden, 2008; Nelson-Becker, 2017).

The situation is changing with more books and journal articles being published on this topic. Professional organizations have supported the formation of groups with particular interests in spirituality, religion, and aging (Royal College of Psychiatrists, 2013; Moreira-Almeida et al., 2016). As an example, North American studies show high levels of religious belief and practice in hospitalized older adults (Koenig, 1998). Religion may also have a salutary effect on a range of physical illnesses, including cardiovascular disease, hypertension, stroke, and various cancers (Koenig, 1998). It may therefore modify the otherwise unfavourable impact that chronic physical illnesses are known to have on the presentation and prognosis of depression. This has significant implications for the assessment, treatment, and prognosis of geriatric depression (Payman et al., 2008). Mental health practitioners working

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with older persons should know how to assess, engage, and address the spiritual and religious needs of their clients.

Residents of rural areas

Rural areas present particular challenges to older people's mental health services, but they are important as often the proportion of older people in rural communities is higher than elsewhere. In some parts of the world, rural areas are extremely remote or at great distances from centres of population. Although the massive growth of urban areas across the world means that the *proportion* of people living in rural areas is falling, the actual *numbers* are still increasing. In 2016, 46% of the global population lived in rural areas (compared to 66% in 1960) but the number rose from 2 billion to 3.4 billion over the same period (<https://data.worldbank.org/indicator/SP.RUR.TOTL>). During this time, the proportion of rural dwellers aged over 65 continued to increase. In addition, particularly in large countries, some populations are not only rural, but also distinctly remote and isolated.

Studies of rural health and social care consistently highlight certain themes, such as poor access to assessment and diagnostic services, sparse public facilities such as daytime activities and paid caregivers, and difficulties with isolation compounded by poor and expensive transport (Marshall et al., 2018). It may be difficult to attract skilled practitioners to work in such areas and they may be at risk of professional isolation when they do. Reliance on families to provide care is likely to be higher and this too may be problematic if younger generations have migrated to urban areas in search of work (Chen, S., et al., 2014). All of these issues will affect people with dementia and other mental health problems, and their families. Other obstacles, such as denial of illness and uncooperative or absent family members, seem to be more frequent in rural settings (Teel, 2004), and rural carers may also be reluctant to use the services available (Ervin and Reid, 2015).

A few studies have examined the circumstances of rural older people, mainly with dementia, in relation to the care they receive. However, most of these reiterate the same difficulties with providing services and there is a relative lack of research on the experience of families or people with dementia themselves (Innes et al., 2011). A Canadian study (Bedard et al., 2004) found that rural caregivers did not experience higher levels of burden even though rural patients had a higher level of behaviour disturbance. In North Wales, carers received most essential services even though levels of services were low, but the main problems were a lack of crisis support and a reluctance to accept long-term care when it was needed (Wenger et al., 2002). Rural caregivers draw upon available social support and often their religious faith, engaging in joint activities where possible (Branger et al., 2016).

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Rural healthcare requires opportunistic and novel approaches to providing services. Working towards 'dementia friendly' rural communities is an important approach (Wiersma and Denton, 2016). The whole system needs to contribute, not just a limited domain such as the aged care service (Lindeman et al., 2014). Any rural dementia outreach service needs to be flexible and responsive in its approach (Clancy, 2015). The organization of primary care is crucial as it is likely to be the hub for contact with outside specialists (Wakerman et al., 2008). For primary care physicians, the main concerns are the distance from specialist expertise and lack of local services, weighed against the possible benefits of being immersed in the local community (Kosteniuk et al., 2014). There remains relatively little research as to what is most useful, and it mainly comprises small descriptive studies (Morgan et al., 2011). The use of technology and telecommunications has obvious potential (e.g. Morgan et al., 2014), though older people are often suspicious of new arrangements based on claims of technical efficiency (King and Farmer, 2009). Instead, they value local services with a personal emphasis and continuity. We need a better understanding of how families living with dementia go about their everyday lives and how they manage within their familiar places and spaces (Marshall, 2018). The way forward seems to be making more use of generic services or everyday environments, e.g. pubs, churches, supermarkets, and hairdressers, to provide flexible and effective support to patients and carers.

Older prisoners

There are significant and increasing numbers of older people among the inmates of prisons and special hospitals. In England and Wales, for example, the numbers of prisoners aged over 60 increased by 120% between 2002 and 2013 to reach a total of 3400, around 4% of all prisoners (House of Commons Justice Committee, 2013). Almost half of older prisoners have some form of mental disorder (Hayes et al., 2012), usually depression, and all forms of mental disorder including dementia are over-represented compared with the rest of the population (Di Lorito et al., 2018a). Identification and treatment of mental disorders in prisoners can be readily overlooked in older prisoners, as they are less disruptive. Many prisoners are in unsuitable conditions with high levels of unmet physical and mental health needs (Di Lorito et al., 2018b) and there are only limited facilities to support them after release. The same applies to special hospital patients who may remain detained longer than necessary because there are no alternatives. Aspects of crime in relation to old age psychiatry are discussed further in Chapter 56.

Intellectual disabilities

Article 25 of the UN Convention on the Rights of Persons with Disabilities (UN, 2006) relates to health care and states that people with disabilities should have the same fair access to health care as the rest of the population as well as having the health needs related to their disability catered for. This has obvious relevance to people with learning disabilities

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as, for example, they have higher rates of early-onset dementia than the general population (see Chapter 47 for discussion of dementia and other mental health problems), and they may also be excluded from consideration by mainstream health and social facilities.

In general, specialist services for people with learning disabilities cover the whole age range, and people who develop dementia continue to be served by facilities with expertise in learning disabilities. Good practice should comprise several areas of activity, including: accurate information about the local population that can inform planning; information and advice for older people with learning disabilities and their families; suitable accommodation and support; encouragement to remain active and maintain social relationships; support with health; and good end-of-life care (Turner and Bernard, 2014). Both service provision and research in this area needs to take into account the voices of people with learning disabilities (Innes et al., 2012). An international meeting on intellectual disabilities and dementia held in Glasgow in 2016 considered three broad topics: human rights and personal resources; individualized services and clinical supports; and advocacy, public impact and policy (Watchman et al., 2017). England and Wales have access to published guidance on care and support of older people with learning disabilities (NICE, 2018a). More attention is also required for people with autism spectrum disorders, whether or not they have a learning disability (Piven and Rabins, 2011). In future, there will need to be more closely defined working arrangements between primary care, learning disabilities services, and older people's mental health services.

Very old people

People over the age of 80 are the fastest growing age group in the world population (United Nations Population Division, 2020). The number is expected to increase by almost six times from 2000 to 2050 to nearly 400 million, by which time 70% of over 80s will be living in LMICs. The ageing of the world population has also seen increases in longevity: by 2050 the number of centenarians will have grown by a factor of 18 since 2000, to an estimated number of 3.2 million. About one million of these will live in Japan, which has claims to be the world's oldest population. Definitions of the 'oldest old' or 'very old people' are variable and the thresholds have increased over time with growing numbers of people living (well) beyond 80. Extreme old age has a universal fascination so it is unsurprising that there are multiple cohort studies of centenarians across the world (Brodaty et al., 2016).

With great age, the patterns of common illnesses change. Circulatory diseases become an increasingly common cause of death, but the age-specific incidence and mortality rates of most cancers decline beyond age 90. With regard to mental health, centenarians scored lower on cognitive tests and were more likely to feel useless and that life was routine and not exciting (Martin et al., 1992), and they were more likely to report a lack of social resources compared to people in their 80s (Randall et al.,

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2010). Variable estimates of the prevalence of dementia in centenarians have been reported, due to such factors as small sample sizes, incomplete ascertainment of the population, exclusion of people in care homes, and relatives sometimes declining to give proxy consent (Brodaty et al., 2016). Longitudinal studies to measure the incidence of dementia are hampered by the high level of attrition due not only to mortality but sometimes by moves to institutional care. There is also a conceptual issue that is usually ignored, which is to question whether the concept of dementia is robust at this age. Given that clinical criteria for dementia are based on decline of cognitive and functional abilities compared with normal values, it is perhaps not well defined what constitutes 'normal' for anyone over 100. Whether there is a survivor effect at extreme old age, with the prevalence and incidence of dementia falling due to selective survival, remains controversial. However, cohort studies of centenarians suggest that decline continues to develop with greater age (Miller et al., 2010).

Within the everyday practice of old age psychiatry, over recent years there has been a noticeable increase in the age of many of the patients referred, with consequent increases in medical comorbidity, physical disability, and complex social care needs. This underscores the importance of providing mental health services for very old people that are comprehensive, interdisciplinary, and allied to provision of physical healthcare, and for the policy and research agendas to address the needs of this group (Denning and Gabe, 2000).

Vulnerable people and safeguarding

The mistreatment of older people is considered in more detail in Chapter 55. From the perspective of old age psychiatry services, there are perhaps two main issues. One of these is a concern with the frequency of abuse of older patients that can occur in institutional settings, including hospitals. There is a sad catalogue of hospital inquiries, which highlight similar themes, such as geographical isolation, low staffing levels, lack of training, lack of nursing leadership, and lack of clinical governance. In England, regulation of health and social care services has been brought together under the Care Quality Commission (CQC), which monitors performance against a set of essential care standards. Safeguarding procedures are led by local authority social services departments. There is also a national Disclosure and Barring Service that provides checks for employers about prospective employees who may be required to work with vulnerable groups, which include mainly children and older people.

The other issue for old age psychiatry services is to participate as part of the multiagency, interdisciplinary response to cases that arise in all settings. This may include various roles, such as psychiatric assessment of the victim and/or the perpetrator, assessments of mental capacity (especially when financial abuse is suspected), and participating in vulnerable people's procedures. Health professionals have an important part to play in detecting and reporting suspected abuse (Cooper and Livingston, 2014). To date, it is mainly physical abuse and neglect that

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have been highlighted. Financial abuse is less often detected and professionals probably need to develop more awareness of its possible occurrence (Manthorpe et al., 2012). In any case of suspected or confirmed abuse, it is necessary to follow due process, including good documentation and communication, but so far evidence for the efficacy of abuse interventions to protect older people is unsatisfactory (Baker et al., 2016).

Improving and maintaining old age psychiatry services

Quality assurance

Quality relates to the care and treatment provided to an individual and to the overall provision of services to a population. Much work in improving quality is about reducing variation in clinical practice so that patients can expect a consistent approach across the whole service. This involves consideration of the whole care pathway or 'the patient's journey'. Examples of this in older people's mental health include:

- 1. Referral criteria.** Ensuring that the service sees those patients who are in most need within a reasonable time scale requires collaboration with referrers, especially primary care. Agreeing thresholds not only for referral but also for discharge from a specialist service is an important way of controlling the caseloads of team members. There may need to be agreed arrangements for the transfer of patients who have been with services for younger adults.
- 2. Standardized assessments.** Many organizations now use standard protocols, for example for memory assessments. These often incorporate, or are augmented by, some of the many standard rating scales that are now available for more specific purposes, such as assessment of cognition and of mood (compiled by Burns et al., 2004).
- 3. Guidelines and protocols for treatment.** Clinical guidelines are systematically developed statements to assist clinicians and patients in making decisions about appropriate treatment for specific conditions. Protocols are written plans specifying the procedures to be followed in providing care for a particular condition. ICPs are locally agreed summaries of practice, based on the best available evidence, for a specific condition or patient group. A care pathway may therefore be the application of a guideline in a practical situation. Guidelines and protocols may cover the whole management of a condition or they may emphasize specific aspects of treatment, e.g. the use of antimentia drugs or psychological treatments. Examples include the NICE dementia pathways (NICE, 2018b).
- 4. Care management.** As mental health problems in old age often require input from a range of professionals and from different agencies, ways of recording, storing, and sharing information are extremely important in ensuring a quality service. In the UK, this is provided through the CPA, which uses standard documentation and

provides a comprehensive record that can be regularly updated and shared with patients and carers. Integrating different systems of care management (and different IT systems) has been the biggest challenge to successful joint working between health and social services.

5. Outcomes. In theory at least, measuring outcomes should be the gold standard for quality, as outcomes should have more direct relevance to patients than do the proxy alternatives of structure and process that are usually measured. However, outcome measurement can be a challenge in old age psychiatry, where often 'bad' outcomes such as death or institutionalization may actually follow episodes of very high-quality care. Routine measurement of outcomes, especially using the HoNOS 65+ (Burns et al., 1999), has become more widespread, particularly as clinical clusters derived from HoNOS 65+ are used as the basis for a tariff-based funding system in mental health. An alternative approach is to use measures completed by patients or proxies (patient-rated outcome measures or PROMs), which are often used alongside patient-rated experience measures (PREMs, discussed in following section).

6. Evaluation of services. Research plays a part in this, but health services research may be complex and costly. RCTs are relatively rare and are designed to address specific research questions rather than assess overall service quality. Instead, a range of approaches are used, of which clinical audit and surveys are probably the most important. Clinical audit is a tool to measure the way in which things are being done assessed against agreed standards, leading to a cycle of making the necessary changes and then re-auditing. The selection of topics for audit may be either 'top-down' (imposed) or 'bottom-up' (chosen) and this may create tensions. There may be limited administrative resources to support the work and the evidence that audit leads to better outcomes for patients is sometimes quite thin. Audits may be local or across organizations.

Effectiveness, safety, and patient experience

Clinical effectiveness is concerned with the extent to which a service follows best practice. In England, the most important source of guidance is the National Institute for Health and Care Excellence (NICE), which produces clinical guidelines on important conditions such as dementia and depression, as well as technical appraisals of new treatments (drugs, therapies, operative procedures, etc.). There is current guidance on dementia (NICE, 2018b) and also a technical appraisal for antidementia drugs (NICE, 2011/2018).

Other aspects of ensuring best practice include clinical audit and medicines management. Audits may be local, but there are also national audits, some of which are mandatory, e.g. the National Confidential Inquiry into Suicide and Homicide by People with a Mental Illness (Appleby et al., 2018). The Royal College of Psychiatrists has established

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a College Centre for Quality Improvement (CCQI), which currently runs over twenty service quality and accreditation projects across mental health, covering the full range of in-patient services and community teams (<http://www.rcpsych.ac.uk/workinpsychiatry/qualityimprovement/ccqipprojects.aspx>). The most relevant of these to old age psychiatry are the Memory Services National Accreditation Programme (MSNAP); the Quality Network for Older People's Mental Services (for mental health in-patients), and the Quality Mark for Elder Friendly Wards (in acute hospitals). Other relevant accreditation projects include crisis teams, ECT, and liaison psychiatry. Each of these has a set of agreed standards and provides inspection visits, feedback, and accreditation for participating services. The CCQI also runs national audits, including one on dementia in general hospitals (Royal College of Psychiatrists, 2017b). Another, the Prescribing Observatory for Mental Health (POMH-UK), benchmarks prescribing practice across member Trusts in order to improve standards and consistency. These have included an audit of the use of antipsychotic drugs in dementia (Barnes et al., 2012).

There are numerous indicators relevant to patient safety, including suicide data, incident rates and incident reporting, and information about falls. Workforce information, e.g. staff satisfaction, sickness rates, and the proportion of temporary staff working in a team, is also highly relevant to patient safety. In recent years there has been more attention paid to safeguarding vulnerable adults, which is of obvious relevance too. Organizations, such as NHS Trusts, that run mental health services will have in place a structure for healthcare governance to report at board level on issues related to quality. There will be board-level responsibility for quality and governance including the Trust's annual quality account.

Patient experience is best directly measured by obtaining feedback from people using the service. This may include questionnaire surveys, but also information from complaints and patient enquiries gives an important indication of the issues that concern patients and families. In old age mental health, carers often act as proxies for patients, especially for people with dementia, but it is important to recognize that the interests of patients and carers do not necessarily coincide (Denning and Lawton, 1998). Other objective measures, such as environmental inspections, length of stay; delayed discharges (for in-patients) and clinical outcomes are also important.

Regulation

The regulatory framework for NHS Trusts in England is provided by two public bodies, NHS Improvement and the Care Quality Commission (CQC). However, the CQC has the main role in relation to quality. It is the regulator not only of NHS services but also of the whole of adult social care (community and residential services), as well as having a remit for compliance with the Mental Health Act. CQC has a framework of 13 fundamental standards that apply to health and social care, covering a full range of issues, from treating people with dignity and respect to

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environmental and staffing issues. Organizations are inspected against these standards and required to amend any failures or concerns that are raised. CQC reports are public documents, as are the quality reports produced by Trusts.

Another important part of the regulatory framework is the Quality and Outcomes Framework that operates in general practice and forms part of the basis for payments to GPs and practices. This sets out a series of indicators across 25 major clinical areas that GPs are expected to meet to obtain the requisite payments. Two areas are relevant to old age psychiatry. There are three indicators for dementia, around maintaining a dementia register, performing appropriate investigations for possible dementia, and keeping patients with dementia under review. The indicators for depression apply to all ages but are concerned with diagnosis, assessment of severity, and review. The introduction of this framework has influenced GP behaviour and encourages GPs to seek a diagnosis for people with possible dementia.

Future challenges

Population change

Probably the biggest single challenge to services for old people across the world is posed by demographic change and the ageing population. This takes different forms in different countries. At present, the developed countries of Europe, Japan, and the US have the highest percentages of people aged 65 and over in their populations. Over the next 20–30 years, numbers of older people will continue to increase, but the increase will be especially in very old people, those aged 85 and above. In contrast, LMICs have lower percentages of old people, but in general their populations are ageing at a faster rate. That is, numbers of people aged over 65 will increase by a greater proportion than in Europe and the US. Moreover, as certain countries (e.g. China, India, and Indonesia) have very large total populations, the absolute numbers of older people in these countries will grow very rapidly.

It is estimated that there are currently around 47 million people in the world with dementia (Prince et al., 2015), a figure predicted to double every 20 years to 115 million by 2050. Already, almost 60% of people with dementia live in LMICs and this proportion will grow to 70% by 2050. The worldwide costs of dementia (US \$818 billion in 2015) amount to more than 1% of global GDP, leading to the often-quoted observation that, if dementia care were a country, it would be the world's eighteenth largest economy (Prince et al., 2015) or, if it were a company, it would be by far the world's largest. Most people with dementia, probably three-quarters of the total number, have not received a diagnosis (<https://www.alz.co.uk/research/statistics>).

An ageing population will be associated with not only more cases of dementia, but also with increased levels of other forms of illness and

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disability, and comorbidity of physical and mental disorders. At the same time, an increasing proportion of older people will affect the national economy, especially if the working-age population is not expanding. This has both economic and manpower effects on the resources that are available for health and social services available to older people. There will, of course, be changes in retirement ages and pensions, which may serve to keep people working for longer.

In the light of these changes, every country should be developing a dementia strategy and putting in place systems that will improve access to diagnosis, information, and help. Information on current dementia plans can be found at <https://www.alz.co.uk/dementia-plans>. Although most of these are currently from Europe or some of the wealthier countries elsewhere in the world, it should be possible, even in the poorest countries, to introduce a coherent strategy using simple interventions based in primary care.

Scientific advances

It is impossible to predict what scientific discoveries may influence the future course of mental disorders in old age. At present, no single development seems likely to have a startling impact upon conditions such as Alzheimer's disease. Better general health may improve dementia and depression, too, though this is difficult to demonstrate. The future availability of pre-symptomatic diagnosis of dementia would have an impact upon the demand for services. Clinicians will become adept at using currently available treatments more efficiently. For example, perhaps Alzheimer's disease may respond better to a combination of several treatments, rather than a single drug such as a cholinesterase inhibitor. It will, however, be difficult to do RCTs to investigate combined treatments as large numbers of patients will be required. In the treatment of depression and psychotic illnesses, improved use of newer antidepressant, mood stabilizing, and antipsychotic drugs, together with use of combined treatments, may bring better outcomes with fewer side effects for many patients.

Dementia has been identified as a global priority for research, though the money spent on it remains relatively limited compared to the amounts spent on cancer and heart disease. In the last few years, there has been progress to increase the numbers of people with dementia participating in research. This includes establishing registers of patients with dementia and ascertaining their willingness to participate in research at the outset, together with the further development of clinical and research networks. There are several international initiatives aimed at creating larger collaborative studies and collecting large databases of potential participants, who have been clinically characterized, e.g. by scans or biomarkers. These include the European Prevention of Alzheimer's Consortium (EPAD); the MRC Dementias Platform UK (DPUK); and the Global Alzheimer's Disease Foundation (GAD). In the UK, the National Institute of Health Research hosts Join Dementia Research (JDR; <http://>

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news.joindementiaresearch.nihr.ac.uk/), a public service where any individual (with dementia or not) can sign up to be contacted about suitable studies, and researchers can use the resource to aid recruitment. At present, about 30,000 people have signed up to JDR, of whom about one-fifth are people living with dementia.

Research into psychosocial aspects of dementia and the lives of older people is also crucial, since the likelihood of curative biological treatments still seems distant. Research is also needed into other mental disorders, such as late life depression, psychosis, and substance misuse. The experience of the millions of people who have dementia *now* needs to be addressed and their needs assessed and met. Thus, at least for the time being, that older people will be most helped by the more effective provision of services. Simple routes of referrals, prompt and efficient assessments, access to specialized treatment when needed, care and support at home wherever possible, all backed up by effective care coordination, are all elements of good services that are supported by evidence. In keeping with trends across the whole of medicine (and, indeed, society in general), the prediction is that the voice of patients and carers as consumers will become more powerful, which, in turn, will influence the type of services available, how they are provided, and the agenda for research.

The impact of technology

Technology has many applications relevant to the lives of older people, and there is burgeoning interest in technology as applied to dementia. There are various ways of classifying technology in relation to dementia, for example, by the type of device (e.g. simple health alarms and memory aids, devices using sensors, and devices using remote technology such as mobile phones or iPads) or by the intended purpose (e.g. to aid cognition or improve mood or whether to enhance safety). A useful approach, which approximately corresponds to the stages of mild, moderate and severe dementia, is based on technology that is (respectively) used *by* the PWD, used *with* them, or used *for* them (Gibson et al., 2016). Examples in these three categories might include, first, independently using an electronic calendar to prompt about appointments; second, the use of personalized memory archives or music playlists; and, third, sensors to monitor movement around the home or to detect falls. The term 'assistive technology' (AT) is often used to emphasize the importance of maintaining function and independence when possible. The term includes the process of assessment and choice as well as any actual devices. AT may also be usefully regarded in three categories: AT that is supplied by public social services following an assessment; 'off the shelf' AT that is usually purchased privately, most commonly by the adult children of the PWD; and 'do it yourself' AT, which is the use of everyday household products modified by the person's families in the absence of any specific alternative AT product (Gibson et al., 2015).

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Meiland and colleagues (2017) reviewed issues around the provision of technologies to support people with dementia living at home and reported several challenges that should be addressed. These include more involvement of end users (people with dementia) in developing products and assessing their usability; better studies of outcomes of using technologies; improved databases of available technologies to improve uptake and deployment; and more consideration of potential ethical issues. There is a distinct lack of well-conducted trials to evaluate the usefulness of various kinds of AT, for example, products to support memory function (van der Roest et al., 2017).

As well as through AT, the quality of services can also be improved in various other ways, e.g. improved online access to information for users and carers. Technology can provide contact with services across long distances, e.g. in rural areas (Bradford et al., 2016). Finally, the potential of electronic care records is yet to be fully realized in many countries (though there are exceptions, such as Finland) as systems in public services may be inflexible or incompatible between organizations. However, advances are possible, e.g. identifying retrospective cohorts from routine health records (Baker et al., 2017) or using free text word searching functions to explore clinical topics, such as drug side effects (Iqbal et al., 2017). In the future, we can also expect that individuals will take a much more active role in their healthcare by taking more ownership of their record. This could transform the current relationship between consumers and providers of services, although it may also raise important issues regarding information governance and confidentiality.

Specialist training in old age psychiatry

The development of specialist curricula and training programmes in old age psychiatry has closely followed the development of clinical services. Formal criteria for old age psychiatry training were first adopted in the UK in 1989, followed by programmes in the US, Canada, and Australasia. In Europe by 2012, there were 11 countries with geriatric psychiatry training programmes (Toot et al., 2012) and ten of these also had specialist continuing professional development for consultants.

The European Association of Geriatric Psychiatry, with the WHO and the WPA Section of Psychiatry of the Elderly, published a consensus curriculum of skill-based objectives for specialist training in old age psychiatry (Gustafson et al., 2003). The curriculum comprised 22 areas of competence and learning objectives. These included clinical skills, such as recognition of mental health problems, history taking, and physical examination; relevant areas of knowledge, including ageing and the mental disorders of old age; treatment, management, and care; and the organization of services. There were some rather specific domains, including end-of-life issues and the abuse of older people. The last few competencies were general topics, such as prevention, teaching, knowledge management, and research. The curriculum is perhaps in need of review: for example, competencies are not operationally defined and

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the curriculum does not provide much guidance as to how they should be assessed. Nonetheless, it has been influential in helping countries set up their own programmes.

Details and requirements for training vary between countries. For example, the entry point into specialization in old age psychiatry in the UK is after three years of core psychiatry training, and consists of a further three years, of which at least two must be in old age psychiatry. In the US, doctors acquire the certificate in psychiatry of the American Board of Psychiatry and Neurology and then undertake an additional year of geriatric psychiatry before sitting the exam for the additional certificate, though there are calls for this additional year to be incorporated in the three years of general psychiatric training in order to improve recruitment in geriatric psychiatry (Kirwin et al., 2016).

In general, however, there has been a trend towards old age psychiatry/geriatric psychiatry both becoming more central to the core curriculum of psychiatric training and acquiring its own identity as a specialty. A good example is provided by Canada, where geriatric psychiatry has recently become required as part of core training for psychiatry, and in 2009 geriatric psychiatry became a recognized subspecialty within the Royal College of Physicians and Surgeons of Canada (Andrew and Shea, 2010). Probably the most detailed curriculum is that developed by the UK Royal College of Psychiatrists (2010, updated 2017, see Fig. 20.2), which covers the competencies required and the relevant assessments for both core and specialist training within psychiatry and old age psychiatry, respectively.

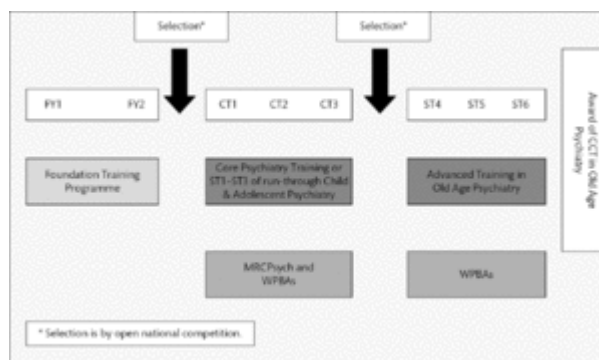


Fig. 20.2

Training pathway to obtain a Certificate of Completion of Training (CCT) in old age psychiatry. FY: foundation year; CT: core training; ST: specialist training; MRCPsych: examination for Membership of Royal College of Psychiatrists; WPBA: workplace-based assessment.

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There are perhaps three big challenges in this area. One is that the curricula usually just relate to old age *psychiatry* and not other mental health professions, for whom training arrangements and competencies are far less developed. A second issue is that there needs to be specific attention on developing clinical researchers in old age psychiatry so that the clinical aspects of mental disorders in old age continue to receive adequate attention alongside basic biological and epidemiological research (Bartels et al., 2010). In England, the National Institute of Health Research (NIHR) has initiated a programme of academic clinical fellowships that offer doctors a proportion of research time while they complete their specialty training, with the aim that they then move on to a higher degree or research fellowship. These posts can be in any specialty, but there is certainly interest in providing posts in old age psychiatry and dementia research. The third challenge is that recruitment can be difficult, since professionals in training may find working with older patients less attractive than with other groups or they are deterred if the sub-specialty training is longer. Research consistently finds that having good experiences working with older people during or before medical school training or other training posts are associated with doctors choosing to work in the specialty (Lieff et al., 2003; Rej et al., 2015). What is probably also required is more flexibility allowing psychiatrists to move into old age psychiatry at a later stage of their career, rather than forcing them to choose irrevocably at too early a stage.

Conclusion

Increasing numbers of older people across the world pose a major challenge to health and social care services, including those involved in mental health. Old age psychiatry has become a mature specialty and there is a considerable evidence base for many of the things that it has to offer. However, there is a paradox in that, at the time that it would seem to be most needed, it also seems to be under threat. Nonetheless, in whatever way services are configured in the future, we will still need well-trained, skilled practitioners who are able to assess and manage conditions such as dementia and depression in older people. Anyone who has these competencies or is in the process of acquiring them should feel confident that they have a major part to play.

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Psychiatric presentations among older people living in low- and middle-income countries

Chapter:

Psychiatric presentations among older people living in low- and middle-income countries

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Introduction

The introduction of operational diagnostic criteria and categories in the Diagnostic and Statistical Manuals of Mental Disorders (DSM) (DSM III, IIIR, IV, 5) (American Psychiatric Association, 1980; 1987; 1994; 2013) and in the International Classification of Diseases-10 (ICD-10) (World Health Organization, 1992) have seen the universalization of psychiatric diagnoses and their use across countries and cultures. This strategy has been also employed for the diagnosis of older people with mental illness. Yet, the use of symptom counts to define psychiatric syndromes without context results in clinical heterogeneity within diagnostic categories, which is often magnified when used in low- and middle-income countries (LMICs) with their diverse environmental milieu. This chapter highlights the different contexts prevalent in LMICs, their impact these contexts

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have on psychiatric diagnosis, and the management of different condition across regions.

Population ageing

The ageing of populations, considered the most significant transformation of the twenty-first century (United Nations, 2015) has been documented across regions, countries and cultures. The total number of persons aged 60 or above is expected to double by 2050 and triple by 2100, rising from 962 million in 2017 to 2.1 billion by 2050, and 3.1 billion by 2100. The great majority of this increase will take place in LMICs: 65% of the increase among older people between 2017 and 2050 will occur in Asia; Africa will contribute 14%, Latin America and the Caribbean 11%, and the remaining 10% will occur in other regions (United Nations, 2017).

The ageing of populations affects diverse aspects of society including labour and financial markets, goods and service sectors like housing, transportation, and social security, family structures, and intergenerational relationships (UN, 2017 report) However, the ageing phenomenon is not a homogenous or uniform process. The differences in base populations and rates of growth and longevity mean that there will be wide variations between regions. The projected increase in older people living in LMICs coupled with limitations in resources in these regions adds complexity and urgency (Ferri and Jacob, 2017). This chapter discusses the issues related to the assessment, diagnosis, and care of older people living with psychiatric disorders in LMICs. It highlights the complexity of the issues, the impact of varied contexts, and the major differences in approaches needed for diagnosis and management.

Dementia

The ageing of populations has also highlighted the importance of age-associated cognitive impairments, including dementia, in older people across regions, countries, and cultures. The number of people living with dementia has been increasing and is estimated to reach 75 million by 2030, with the majority living in LMICs (Alzheimer's Disease International, 2015).

DSM-5 recommends that major neurocognitive disorder (termed dementia in earlier editions) is diagnosed in the presence of significant cognitive decline from a previous level of functioning in one or more cognitive domains, which include complex attention, executive function, learning and memory, language, perceptual-motor, and social cognition (APA, 2013). These deficits interfere with independence in everyday activities and evidence of decline is based on information from a knowledgeable informant/clinician and preferably documented by neuropsychological testing. These cognitive deficits do not occur exclusively in the context of delirium and are not better explained by another mental disorder (e.g. major depression, schizophrenia).

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DSM-5 recommends the use of neuropsychological testing or, in its absence, another quantified clinical assessment to document impairment in cognitive performance (APA, 2013). It recommends comparison with population norms appropriate to the patient's age, educational attainment, and cultural background. It suggests a diagnosis of major neurocognitive disorder for performance more than two standard deviations below the population norm or less than the third percentile. Nevertheless, DSM-5 also acknowledges that neuropsychological testing is not available in all settings, that neuropsychological thresholds are sensitive to the specific test(s) and norms employed, as well as to test conditions, sensory limitations, and inter-current illness. It also suggests specific 'bedside' assessments to objectively document current performance in settings where such testing is unavailable or not feasible. The absence of population norms in many LMICs complicates issues (Jacob, 2014a,b).

Prevalence

Estimates of the total numbers and proportion of older people living with dementia across regions and countries show an increasing trend. However, differences between populations have been documented. Population-based studies on dementia prevalence have been done around the globe. Prevalences seem to be lower in India (1.36% to 3.50%) compared to the high-income country (HIC) data (5.9% to 9.4%) (Chandra et al., 1998; Ferri et al., 2005). A systematic review of the global prevalence of dementia showed that age-standardized prevalence varied from 2.1% in sub-Saharan Africa to 8.5% in Latin America (Prince et al., 2013). Systematic reviews have also documented the high prevalence of undetected dementia, particularly across LMICs (Lang et al., 2017).

True differences in population prevalence exist and are attributed to differing genetic and environmental factors, life expectancy, duration of disease, and age-specific incidence. However, variations in prevalence data may also be due to the use of different data collection procedures (one stage/two stage), assessment schedules, diagnostic criteria, and cultural conceptions of the condition (Ferri and Jacob, 2017).

Diagnosis

It has been well recognized that low or absent education impacts cognitive assessment in general (Cherbuin et al., 2008) and in LMICs in particular (Lopes, 2012; Noroozian et al., 2014). The 10/66 Dementia Research Group examined the impact of education and age on performance in dementia assessments and developed strategies for adjusting for these (Prince et al., 2003; 2004). They employed a standardized methodology to assess the prevalence of dementia in many LMICs (e.g. Latin American countries, China, and India) in order to produce data, which is comparable across regions (Prince et al., 2004). However, a detailed analysis of data from Vellore, India, which was part of the consortium, demonstrated wide variations in prevalence depending

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on the diagnostic criteria used. The prevalence of dementia was 63.4%, 21.2%, 10.6%, and 0.8% with the Geriatric Mental State (using AGE-CAT), the original 10/66 diagnostic algorithm, the education adjusted 10/66 algorithm, and according to Diagnostic and Statistical Manual IV (DSM-IV) criteria, respectively (Jacob et al., 2007b). Investigations from Africa comparing DSM-IV criteria with 10/66 criteria have also demonstrated significant differences (Paddick et al., 2013, 2015). The 10/66 Dementia Research Group has also acknowledged the wide variation found in prevalences based on specific diagnostic criteria (Llibre Rodriguez et al., 2008).

Information variance (e.g. different informants, interview schedules) is a common reason for observed differences in prevalence; variations in diagnostic criteria also contribute to massive differences in the threshold for the condition, and the number and the type of patients identified (Jacob et al., 2007a; Jacob, 2014b). While there is general agreement on the major criteria for the diagnosis of dementia, minor variations in information and criteria can result in wide variations in the patients identified and pose a major problem for cross-national comparisons.

The diagnosis of dementia is also complicated by the fact that newer criteria differ from standards used in the past. DSM-5 has made significant changes to its diagnostic criteria for dementia (now termed major neurocognitive disorder) (APA, 2013). It has expanded cognitive domains, which now also include complex attention and social cognition. The clinical interview schedules and instruments used to diagnose dementia do not routinely assess these domains and/or include them in their diagnostic algorithms. Clinical information and the results of neuropsychological tests are also necessary for a definitive diagnosis of neurocognitive disorders. DSM-5 also demands a comparison of the person's individual performance in neuropsychological tests with population norms, adjusted for age, education, and cultural background. As mentioned, the absence of population norms and the lack of resources to conduct detailed neuropsychological tests in LMIC hamper cross-site comparisons (Ferri and Jacob, 2017; Jacob 2014b). In addition, the clinical continuum of age-related cognitive decline, mild cognitive impairment (minor neurocognitive disorder), and dementia make the task of dichotomous demarcation, to identify dementia, difficult (Jacob et al., 2007b; Jacob, 2012b, 2014b).

The impact of cognitive decline on a person's daily function is also dependent on their milieu, which includes family expectations of their behaviour and involvement in family life, socioeconomic circumstances, level of social support, cultural roles, and social responsibilities. Consequently, variations in the milieu will affect the impact of impaired functioning, resulting in differential measured disability and handicap. In addition, cognitive impairment is more difficult to identify in settings where memory loss is considered part of normal aging, in contexts where older people face fewer cognitive demands in everyday life (e.g. joint families common in some LMICs) and where low education poses

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significant challenges to cognitive assessments (Patel and Prince, 2001; Jacob et al., 2007b).

Screening instruments and strategies

Several instruments have been employed to screen patients for dementia in the community (Milne et al., 2008). Many screening instruments designed and developed in HICs have attempted to reduce the impact of education level, ethnicity, and culture. However, the use of items, which are region and culture specific (e.g. the recall of information including dates, paper-and-pencil tests, details related to finance and travel) makes it difficult for people without cognitive impairment in LMICs to fare well in these tests (Jacob, 2014b).

Because of the high rates of underdiagnosis worldwide, there is currently a strong call to increase diagnosis rates (Jacob, 2016). However, there are several challenges to be overcome regarding any potential screening programme to help increase identification (Stanley, 2009; Chambers et al., 2017). These include that: (i) many instruments, including the commonly used Mini-Mental Status Examination, are influenced by education and by culture, making them inappropriate for use in societies with low literacy (Mitchell, 2009); (ii) the education and culture free screening tests, which employ activities of daily living rather than paper and pencil tests, do not systematically test multiple cognitive domains; (iii) even screening instruments with good sensitivity and specificity, when used in situations of low prevalence (e.g. community and primary care) result in high false positive rates and low positive predictive values as these are dependent on prevalence (and incorrect identification of people with dementia can have long-term consequences including stigma, loss of employment, and autonomy); (iv) health systems might not have the capacity to increase screening. Therefore, at the moment, screening should only be employed in people with symptoms of cognitive impairment, rather than using it in the general population, where prevalence is much lower, making these instruments perform poorly and result in misclassification.

A recent systematic review and meta-analysis concluded that while numerous tools for assessment of cognitive impairment in low-literacy settings have been developed, and tools developed for use in HICs have also been validated in low-literacy settings, most tools have been inadequately validated (Paddick et al., 2017). They conclude that at present no screening test can be recommended for use (Paddick et al., 2017).

The changes in the DSM-5 standards for dementia (APA, 2013), the expansion of cognitive domains, and the need for the establishment of local norms mandate a review of previously validated and routinely employed screening tools. A recent study attempting to validate existing instruments (e.g. MMSE, Vellore Screening Instruments for Dementia (VSID)) reported different screening thresholds dissimilar from those

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originally recommended for these instruments; it also recorded different indices of efficacy, i.e. sensitivity and specificity (Varghese et al., 2018). These findings demand a recalibration of all existing instruments for use with the new DSM-5 standards. They also suggest the need to recalculate cut-offs/thresholds for screening.

Most of the available screening instruments were developed long before the advent of the DSM-5 standards. The MMSE uses simple screening questions to evaluate comprehension, reading, writing, orientation, and drawing abilities, which were the gold standard for diagnosis of dementia in the 1970s (Folstein et al., 1975). VSID employs activities of daily living related to the DSM-IV diagnostic criteria/domains (memory impairment, agnosia, aphasia, apraxia, and loss of executive function) (APA, 1994) against which they were validated (Stanley et al., 2009). Essentially all screening instruments, when initially designed, take the available gold standard of diagnosis and attempt to simplify the diagnostic process and employ proxy questions/tasks to identify similar dysfunction (Díaz-Orueta et al., 2017). Consequently, major changes in gold standards mandate the need to redesign screening instruments. The increased scope of the DSM-5 symptom criteria for diagnosis of neurocognitive disorders demands the need for a reappraisal of screening and confirmatory strategies. There is a definite need to develop screening instruments which evaluate all dimensions of cognitive impairment included in the DSM-5 criteria, which then have to be validated against the new standard in large populations.

Yet, screening instruments and strategies, even those with good sensitivity and specificity, do not perform well in situations with a low prevalence of the condition (Chambers et al., 2017). Predictive values are prevalence dependent and screening all people, when the prevalence of dementia/mild cognitive impairment is low, is bound to result in high false positive rates. Even good screens for dementia will necessarily have to be judiciously used, as they will perform poorly if employed in community and population surveys (Stanley et al., 2009). However, their predictive values will improve when used to screen people who complain of cognitive problems and those whose caregivers report such difficulties.

Correlates

Many factors associated with dementia in HICs have also been documented in LMICs. These include: increased mortality (Prince et al., 2012a; Wang et al., 2010), female sex (Ochayi and Thacher, 2006; Cheng et al., 2014), advanced age (Ochayi and Thacher, 2006; Prince et al., 2012a), hypertension (Ogunniyi et al., 2011), diabetes mellitus (Salas et al., 2016), APOE ϵ 4 genotype (Rodriguez et al., 2014), smoking (Ferri et al., 2011), low fish and meat consumption (Albanese et al., 2009), traumatic brain injury (Khan et al., 2015), sleep complaints (Mazzotti et al., 2012), frailty (At et al., 2015; Llibre Rodriguez et al., 2018), neuropsychiatric symptoms (Acosta et al., 2017), incontinence, hearing impairment, mobility impairment, and under-nutrition (Prince et al.,

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2011b), weight loss (Albanese et al., 2013b), smaller arm and waist circumferences (Taylor et al., 2012) and shorter leg length and skull circumference indicative of lower early-life nutrition (Prince et al., 2011a), and contemporaneous low blood pressure (Albanese et al., 2013a).

Disability

Disability among older people has been measured across LMICs (Sousa et al., 2010). A 10/66 Dementia Research Group study demonstrated that dementia and other biomedical determinants (e.g. stroke, limb impairment, arthritis, eyesight problems, gastrointestinal disorders) were the leading cause of disability among older people (Sousa et al., 2009). However, a reanalysis of 10/66 data from India, which included environmental variables in the multivariable model, identified many social and economic factors as significantly contributing to disability (Duba et al., 2012). These included advanced age, illiteracy, hunger, poor nutrition, and the cost of travel to primary health facilities. There is a need to focus on local contexts and modifiable risk factors to design appropriate public health policies and interventions for older people in LMIC (Llibre Jde et al., 2011).

Mild cognitive impairment

Mild cognitive impairment (MCI; minor neurocognitive disorder) is diagnosed in the presence of cognitive decline from a previous level of functioning in one or more cognitive domains included in the DSM-5 (APA, 2013). These deficits interfere with independence in everyday activities, based on information from a knowledgeable informant or documented by neuropsychological testing. Furthermore, the deficits do not occur exclusively in the context of delirium and are not better explained by another mental disorder (e.g. major depression, schizophrenia). The recommended norms for minor neurocognitive disorder are fixed between the third and sixteenth percentile or between 1–2 standard deviations. DSM-5 recommends the use of neuropsychological testing or in its absence, another quantified clinical assessment to document impairment in cognitive performance (APA, 2013). It recommends comparison with population norms appropriate to the patient's age, educational attainment, and cultural background. Nevertheless, DSM-5 also acknowledges that neuropsychological testing is not available in all settings, that neuropsychological thresholds are sensitive to the specific test(s) and norms employed, as well as to test conditions, sensory limitations and inter-current illness. It also suggests specific 'bedside' assessments to objectively document current performance in settings where such testing is unavailable or not feasible. As described for dementia, the absence of population norms in many LMICs complicates issues (Jacob, 2014b).

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MCI has been reported from across LMICs (Nie et al., 2011; Baiyewu et al., 2012; Wang et al., 2015; Villareal et al., 2016). MCI was examined in Latin America, China, and India using 10/66 standardized methodology and algorithms (Sosa et al., 2012). The crude prevalence of amnesic MCI (aMCI) ranged from 0.8% in China to 4.3% in India. Country differences changed little (range 0.6%–4.6%) after standardization for age, gender, and education level. Pooled estimates suggested that MCI was significantly associated with male gender and fewer assets but was not associated with age or education.

Mild cognitive impairment may be more difficult to identify in settings where memory loss is considered part of normal aging, in contexts where older people face fewer cognitive demands in everyday life (e.g. joint families common in some LMICs), and where low education poses significant challenges to cognitive assessments (Patel and Prince, 2001; Jacob et al., 2007b).

Delirium

Delirium is characterized by a disturbance in attention and awareness (reduced orientation to the environment), often of short duration, and with an abrupt onset. Disturbance of cognition (e.g. memory deficits, disorientation, language, visuospatial ability, or perception) may also be present (APA, 2013). Its close association with medical illness is reflected in incidence and prevalence estimates that vary widely depending on clinical setting. Substance withdrawal, medication-induced delirium, and delirium with multiple aetiologies are also common. The prevalence of delirium in hospital settings is high compared to that present in the general population and in community locations.

Instruments to recognize delirium have been validated and used in LMICs (Shyamsundar et al., 2009; George et al., 2011). While delirium, as a clinical presentation, has been identified across LMICs (and often in the medical context and hospital settings; see Säll et al., 2009; Lahariya et al., 2014; Tanaka et al., 2015; Xing et al., 2017), most of the studies on the subject do not focus on older people. A systematic review identified only two studies of delirium among older people from Africa (Paddick et al., 2015). Regional variations in aetiology and medical comorbidities that cause delirium, and variations in the manifestation of the clinical syndrome, demand further study.

Psychosis

Psychosis is also a common presentation among older people. The later onset of psychosis often mandates a careful clinical examination and investigations to rule out underlying causal medical, endocrine, and neurological conditions. Late-onset psychosis is often characterized by a predominance of psychosis with preservation of affect and social functioning. The relationship of such psychosis to schizophrenia diagnosed prior to mid-life remains unclear. Studies on late-onset

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psychosis form a small minority of all research efforts related to psychosis in general, and particularly in LMIC settings.

Socioeconomic and cultural factors play an important role in clinical presentations. Ideas that appear to be delusional in a particular culture (e.g. witchcraft) may be common in another. Linguistic variation in narrative styles across cultures mandate culturally sensitive assessments. Evaluating pseudo-hallucinations and overvalued ideas requires cultural competence on part of clinicians. Soares and colleagues (2015) examined psychotic symptoms in a Brazilian community sample and documented its correlation with lower cognitive scores, lower education, and lower socioeconomic status, as well as higher medical comorbidity. A study from Nepal recorded much lower rates of older people hospitalized in psychiatric facilities, compared to HIC rates and to younger people from the area, suggesting poor delivery of care to this group (Aich et al., 2012).

At least one behavioural and psychological symptom of dementia was reported in 70.9% of the participants in the population studies of the 10/66 Dementia Research Group undertaken in Latin America, China, and India, with schizophreniform/paranoid psychosis diagnosed in 10.9% of the sample (Ferri et al., 2004).

Depression and anxiety

Depression and anxiety with onset in late life are common and documented across LMICs. The World Health Organization's 'Study on global AGEing and adult health (SAGE)' documents a cross-national prevalence of late-life depression of 4.7% (95% CI: 1.9%–11.9%) (Brinda et al., 2016b). Female gender, illiteracy, poverty, indebtedness, past informal-sector occupation, bereavement, angina, and stroke had significant positive associations, whereas pension support and health insurance showed significant negative associations with late-life depression.

These disorders also commonly co-occur with dementia in older people. Depression (45.3%), apathy (37.7%), appetite change (24.5%), irritability (22.6%), delusions (22.6%), anxiety (18.9%), and agitation (17.0%) have been reported among older people in Nigeria, particularly those with cognitive impairment (Baiyewu et al., 2012). While at least one behavioural and psychological symptom of dementia (BPSD) was reported in 70.9% of the participants of the 10/66 population studies, depression syndromes (43.8%) were most common (Jacob, 2012a) followed by anxiety neurosis (14.2%) (Ferri et al., 2004).

The prevalence of co-occurring anxiety and depression syndromes ranged between 0.9% and 4.2% across 10/66 data collection sites. Gender, socioeconomic status, urbanicity, and physical comorbidities were associated with the different comorbid states and these disorders were linked to higher disability scores (Prina et al., 2011a). However, age- and gender-standardized prevalence of anxiety varied greatly across 10/66

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sites, ranging from 0.1% in rural China to 9.6% in urban Peru. Age, gender, socioeconomic status, and comorbid physical illnesses were all associated with a GMS/AGECAT diagnosis of anxiety, as was disability (Prina et al., 2011b). Much of the evidence suggests the need to manage psychosocial and economic contexts in addition to medical comorbidity among older people in order to reduce symptoms of depression and anxiety in late life.

Substance use

It is now recognized that misuse and addiction to alcohol, prescription medication, and illicit drugs, although not often studied among older people, is an invisible epidemic in many countries. The increasing size of the older cohorts poses particular challenges. Physiological changes with aging and age-related factors have led to the setting up of lower recommended limits of alcohol use among older people. Under-reporting of use and the use of prescription and over-the-counter medication is also common among older people.

Alcohol use has been documented among older people living in LMICs (Kim et al., 2007; Zhou et al., 2014; Martinez et al., 2014). Nadkarni and colleagues (2011) documented the significant presence of harmful alcohol use among older people living in the Dominican Republic and its adverse impact on family and carers, which was not accounted by disability but explained by behavioural problems. Zhou and colleagues (2014) reported on the risk of alcohol and tobacco use and its association with dementia among older people living in China. A high degree of concordance of smoking and drinking habits has been documented among older couples living in Latin America, which was explained by the size of their social networks rather than by their socioeconomic circumstances (Machado et al., 2017). Similarly, medication overuse has been documented across LMICs (Find et al., 2015; Kamuhabwa and Lugina, 2010). While substance misuse and dependence are often managed as an individual issue requiring specific treatment and psychological intervention, there is much to be said for the use of public health approaches to reduce their use in LMICs (World Health Organization, 2014; 2017).

Suicide

Higher suicide rates have been traditionally reported among older people. Suicide has also been associated with mental illness. Completed suicides, suicidal attempts, and ideation have been recorded across LMICs. Borges and colleagues (2015) found a lifetime prevalence of suicide ideation of 13.5% and a two-week prevalence of 4.2% in a community sample of older people in Mexico. The common factors associated with both these outcomes were having a large number of physical disorders, depression and anxiety, and screening positive for psychosis.

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Very high annual suicide rates of 189 per 100,000 for people over 55 years of age have been reported from India (Abraham et al., 2005). The age-specific suicide rate for men and women increased with age. Hanging (52%) and poisoning with organophosphorus compounds (39%) were the commonest methods employed for committing suicide. Significantly, more women chose drowning or burning as suicide methods than men, who were more likely to choose poisoning or hanging.

Suicide, a common cause of death in many LMICs, has often been viewed through a medical/psychiatric lens (Jacob, 2017b). However, recent studies have documented low rates of mental illness and higher rates of contextual stress. A systematic review that examined the association between suicide and poverty in LMIC documented a positive association (Iemmi et al., 2016). It also acknowledged a positive association between non-fatal suicidal ideation, behavioural symptoms, and poverty and argued for the potential benefit of addressing economic poverty within suicide prevention strategies, with particular attention to both chronic poverty and acute economic events. Recent studies from India (Manoranjitham et al., 2010) and from China (Zhang et al., 2010; Li et al., 2008) have also shown that the majority of the people who kill themselves are distressed secondary to their psychosocial context and only a small minority have severe mental illness. While people with severe mental illnesses do complete suicide, their contribution to population rates is much less significant than that seen in HICs. The absence of a social security net, which seems to be crucial in managing psychosocial and economic distress, may explain the differing rates of suicide and the rates of serious mental disorders among those who kill themselves in high-income and emerging economies.

While individual interventions and psychiatric inputs can prevent suicide in people identified to be at risk, their impact on population rates of suicide is yet to be demonstrated. Consequently, public health approaches have also been advocated. For example, ingestion of pesticides is a common method of suicide in settings where these are readily available and kept in accessible domestic locations (Abraham et al., 2005). It has led to research, encouraged by manufacturers of pesticides, which focused on evidence that providing safer methods of storage (e.g. a double locked box) (Hawton et al., 2009) and the use of pesticide banks (i.e. a secured central storage facility) (Vijayakumar et al., 2013) to reduce impulsive suicide attempts and fatalities. Nevertheless, such focus belies the fact that extremely lethal pesticides banned in HICs are sold by multinational corporations and are freely available in most LMICs. These strategies shift the responsibility for suicide from large businesses, which refuse to change practices in order to maximize profits, to individuals. While selective approaches like the banning of lethal WHO Class I organophosphorus insecticide in Sri Lanka has reduced hospital admissions, the use of Class II compounds means continued deaths by pesticide self-poisoning (Eddleston et al., 2012).

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While interventions have shown a reduction in method-specific or site-specific rates, there is no firm evidence to suggest an overall reduction in suicide (Jacob, 2017b). The reductions in suicide reported in some countries have more to do with secular trends and improvements in living standards than specific suicide prevention programmes. Social determinants of health and mental health demand public health interventions in order to reduce inequity and provide social justice, which in turn may prevent suicide among vulnerable people.

Suicide, when viewed through a medical/psychiatric lens, medicalizes social and personal distress and suggests individual and medication-based treatments. There is a definitive need to examine suicide in LMICs from a public health perspective and argue for the need for population-based social and economic interventions. (Jacob, 2017b).

Carer burden and health expenditure

The costs of psychiatric problems among older people and carer burden have been studied in LMICs. A recent study (Ferretti, 2018) on the costs of dementia in Brazil showed that 56.6% of total dementia costs was attributable to informal care costs. In this study, progression of the disease, which was associated to caregiver burden, had a significant influence on the economic impact of the disease. The impact of dementia on the mental health of relatives and carers of older people living in LMICs has also been documented. Depression and high strain scores have been recorded among carers of people with dementia in the 10/66 Dementia Research Group studies (Prince, et al., 2012b; Brinda et al., 2014). Women carers reported more strain than men; carer strain was associated with the presence of behavioural and psychological symptoms of dementia (BPSD), severe dementia, higher disability, incontinence, need for care, and time spent caring. There was tentative evidence for a protective effect of having additional informal or paid support.

Inequitable service access and the cost of care for older people also contributes to carer burden. Increasing out-of-pocket health expenditure among older people has been documented and worsens the inequitable access to essential health services in LMICs (Brinda et al., 2012). Male gender, poor sanitation, diabetes, tuberculosis, malaria, respiratory ailments, gastrointestinal diseases, dementia, depression, and disability were associated with higher out-of-pocket expenditure. Illiteracy, tuberculosis, diabetes, and dementia increased the risk for catastrophic health expenditure, while pension schemes protected against it. Income inequalities were associated with inequities in education, disease prevalence, and access to safe water, sanitation, and nutrition. It highlights the need for equitable health services and policies, focusing on both medical and social determinants. Socioeconomic disparities in health and health care are major concerns in many LMICs (Brinda et al., 2016a,b). The achievement of health equity demands strategies beyond

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health policies, to include pro-poor, social welfare policies among older people.

Health systems

Health systems play a significant role in the care of older people and impact health care delivery. Dementia, for example, is under-recognized, under-disclosed, under-treated, and under-managed, particularly in LMICs (Ferri and Jacob, 2017; Lang et al., 2017). The WHO (1990) and the 10/66 Dementia Research Group (ADI, 2016; Shaji et al., 2002) recommend the strategy of employing community health workers to identify mental illnesses in general, and dementia in particular, in resource-poor settings. However, in India the use of community health workers to identify people with dementia in the population resulted in a very high false positive rate (Jacob et al., 2007a).

The reasons for the failure of the strategy include the fact that disorders with low prevalence at the community level cannot be diagnosed accurately unless a referral system is in place. A tiered organization (e.g. health worker, public health nurse, physician, psychiatrist/neurologist) that screens, confirms, and refers people at risk up a pathway of care is therefore required for improving the overall accuracy of the system. The failure to put in place such a diagnostic system, which employs health personnel to filter cases at multiple levels, has contributed to the failure of community psychiatry programmes across LMICs (Jacob, 2011) that aimed to identify and manage mental disorders including dementia. There is a definite need to put in place a tiered network if screening and management programs are to be successful (Jacob et al., 2007a).

Health services in LMICs are beset by multiple and complex problems, including poor infrastructure, overburdened systems, inappropriate training for health professionals, professional apathy, limited finances, impoverished environments, and low morale of primary health-care staff. The problems are compounded by substantial differences in primary and tertiary care approaches to mental health and illness and include differences in settings, patient profiles, and physician perspectives (Jacob, 2014a; Jacob and Patel, 2014). It is important to acknowledge the complex realities of primary care in LMICs when advocating for the introduction of mental health care into primary care.

Care

Care of older people with psychiatric problems is complex, particularly in resource-poor settings. The progression of the disease alters care needs over time in people living with dementia; other psychiatric presentations may also require continual assessment and a continuously tailored management approach to deal with the clinical changes and changed contexts (ADI, 2016). While health care models that focus on task-shifting and task sharing have been discussed in HICs, the challenges are even

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more complex with the limited resources found in LMICs (Ferri and Jacob, 2017).

The identification of the critical role of local and social determinants in respect of disability, and the paucity of medical interventions to reverse the pathology of dementia, mandate the need for psychosocial support, accommodation, and nursing care as the mainstays of management (ADI, 2016). In reality, reduced public health expenditure, the absence of social security and the limited access to universal health care in most LMICs, as well as the lack of formal and institutional care for dementia, place a huge burden on relatives and carers (Ferri and Jacob, 2017) and result in increasing out-of-pocket expenditure (Jacob, 2017a). While informal care and family support are crucial, organized services for older people living in LMICs will reduce the costs and burden of care. However, overburdened and under-resourced public health systems, low staff morale, poor training, and limited expertise in mental health result in poor care for older people. There is a need to integrate social and health intervention programmes to provide optimal care for older people (Alzheimer's Disease International, 2016).

Need for a contextual understanding

The mental health issues facing older people in LMICs and the different approaches this chapter describes need to be considered taking into account their day-to-day lives and the particular characteristics of the local settings. The success of programmes in HICs and their replication in successful projects in LMIC do not necessarily mean that they can be scaled up and be effective when rolled out to larger populations. The distinctive context of care for older people in LMICs requires tailored solutions to the problems they face. Context and local knowledge are critical to understanding health and illness and structures of care (Jacob, 2017c).

Direct comparisons between LMICs and HICs of context, presentations, burden, and services may not be appropriate. Medical and non-medical approaches and public health strategies should all be employed to relieve the suffering related to mental distress and illness among older people. The issues call for a shared perspective, which should be negotiated not only with people with mental illness, but their families and local communities as well.

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Primary care management of older people with mental health problems

Chapter:

Primary care management of older people with mental health problems

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Introduction

This chapter discusses the presentation and primary care management of the commonest mental health problems in older people. It presents cases drawn from the authors' real-life practice to represent clinical presentations and management within primary care and liaison with secondary care and the wider team. It discusses the management of patients largely within reference to UK primary care systems and policy, but the international readership should find parallels within their own healthcare systems.

Primary care management of older people with mental health problems

Primary care in the UK

In the UK, primary care services are an integral part of the National Health Service (NHS) in which general practitioners (GPs) work as independent contractors. People are required to register as patients with a general practice; currently, a practice determines its boundaries and only accepts patients who reside within this area. The GP works as a generalist and a provider of personal, primary, and continuing care to individuals, families, and a practice population, irrespective of age, gender, ethnicity, and problem. In England, the Health and Social Care Act 2012 requires GPs to undertake a commissioning role with greater involvement in the purchasing of local services for their patients in addition to their service provider role.

GPs increasingly work with a range of healthcare professionals in a multi-disciplinary primary healthcare team. The team includes a practice manager and administrative staff, practice nurses, and nurse practitioners or specialist nurses. Community nurses, such as district nurses, active case managers, Macmillan nurses, and health visitors may be co-located or linked with a group of practices. Team working is essential in order to manage the complex demands placed on general practice, which are partly due to caring for an increasingly ageing population with chronic and multiple health problems. The greater emphasis on preventative care, the transfer of clinical responsibility for some chronic diseases from secondary to primary care, and the shift in service provision in order to deliver care closer to patients' homes has contributed to these demands.

The implementation of a new General Medical Services (GMS) contract in 2004 fundamentally changed the way in which GPs work in the UK. The contract defines essential primary care services and optional enhanced services that are additionally remunerated. The contract links achievements in clinical and nonclinical care quality to financial rewards, through a Quality and Outcomes Framework (QOF) derived from evidence-based care (Gillam et al., 2012). The system encourages the delivery of optimum care in clinical domains, with emphasis on chronic disease management.

Common mental health problems in older people in primary care

Primary care is on the front line in dealing with older people's mental health, supporting families and managing people with complex comorbidities. Older people consult almost twice as often as other age groups: 22% of older people will have attended their GP within the last two weeks and 40% may have a mental health problem (NHS Digital, 2007). This chapter now considers in detail the initial management of the most common mental health problems encountered in older people in primary care. These include delirium, delusions, depression and anxiety, and dementia. These topics are considered from a primary care perspective but are also covered in other chapters throughout the book

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(delirium, Chapter 37; psychosis, Chapter 43; depression and anxiety, Chapter 38, 39, and 42; dementia, Chapters 28–36).

Delirium

Delirium is common in hospital patients (10–20% in all medical patients but up to 40% in people with cancer), but it is becoming increasingly common in older people in the community (Young et al., 2010).

Clinical presentation

Delirium is a syndrome comprising disturbance of consciousness (often manifest as impaired attention or concentration), cognitive deficits (such as memory, orientation, and language problems), and disturbed sleep–wake cycle; perceptual problems such as visual and auditory hallucinations and delusions; behavioural disturbance (such as restlessness, agitation, and apathy) and alterations in affect (such as fear), in addition to alterations in social behaviour (e.g. lack of cooperation with reasonable requests, withdrawal, and alterations in communication) (Table 22.1).

Table 22.1 How to differentiate between delirium, depression, and dementia.			
	Delirium	Depression	Dementia
<i>Onset</i>	Acute	Variable	Insidious
<i>Duration</i>	Days	Variable	Months to years
<i>Course</i>	Fluctuates	Possible diurnal variation (worse in morning)	Slowly progressive (though may be stepwise)
<i>Consciousness</i>	Impaired and fluctuating	Unimpaired	Clear at onset
<i>Attention and memory</i>	Inattentive; Poor memory	Poor concentration, sometimes complaining of poor memory	Poor memory but without inattention
<i>Affect</i>	Variable	Depressed;	Variable

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		Loss of interest and pleasure in usual activities	

The term delirium is synonymous with 'acute confusional state'. Onset is often sudden (hours or days) and fluctuation is a hallmark; a useful mnemonic is the four 'T's (Crausman, 2004):

1. Intermittent impairment of cognition
2. Inattention
3. Incoherent thought
4. Impaired consciousness.

The differential diagnosis includes depression, which can be associated with agitation or withdrawal, and dementia (Table 22.1).

Three main subtypes are recognized:

1. *Hyperactive delirium* (hallucinations, delusions, agitation, and disorientation).
2. *Hypoactive delirium* (cognitive impairment with apathy or withdrawal, less often accompanied by hallucinations and delusions).
3. *Mixed delirium* (displays both hypoactive and hyperactive features).

The third form can easily be overlooked in older patients.

Delirium can be triggered by a wide range of factors (Box 22.1), but those with pre-existing cognitive impairment or dementia are at increased risk. Age is a risk factor, and people in nursing and residential homes are also at increased risk. Factors frequently combine, e.g. a person with dementia who becomes constipated or develops a urinary tract infection. Delirium is common in end-of-life care and poor management will contribute to a poor-quality death and distress for carers.

Box 22.1 Risk factors and precipitants of delirium

Socio-economic

- Age (>65 years)
- male gender
- little contact with relatives
- institutional care

Physical

- Parkinson's disease
- Pain

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- Previous stroke
- Constipation
- Cancer
- Anaemia
- Metabolic (e.g. thyroid disorders, diabetes)

Acute physical event

- Any infection but particularly urinary tract infection (UTI) or lower respiratory tract infection (LRTI)
- Myocardial infarction
- Fracture
- Dehydration
- Organ failure

Mental health

Pre-existing dementia

Medications

- Hypnotics, analgesics
- Anti-Parkinson's disease drugs
- Drug interactions and polypharmacy
- Side-effects causing electrolyte disturbances

Sensory impairment

- Visual impairment
- Hearing impairment (can be as simple as a lost hearing aid)

Functional impairment and disability

- Malnutrition
- Dehydration

Environmental change

House move

Other:

- Shock
- Sepsis

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- Surgery
- Sleep deprivation

Assessment

Delirium is a symptom of underlying problems, and not a diagnosis in itself. The diagnosis is made on the history from the patient and a collateral history from informed observers (e.g. family member or caregiver), plus a physical examination to look for physical cause. Investigations in primary care should include: mid-stream specimen of urine (MSU), full blood count (FBC), urea and electrolytes (U&Es), liver function tests (LFTs), C-reactive protein (CRP), thyroid function tests (TFTs), and glycosylated haemoglobin (HbA1C). The practitioner should consider the need for other investigations, such as electrocardiogram (ECG) and chest X-ray (CXR). If more intensive investigation is thought necessary or the patient is at risk, then admission to hospital should be considered.

It is important to assess cognitive function, both as a baseline and to assess fluctuation. If the person is in hospital, use of the Confusion Assessment Method (CAM) (Inouye 1990) or Observational Scale of Arousal (OSLA) (Tieges, 2013) may help to distinguish between delirium, or delirium imposed on underlying dementia (NICE, 2010).

Principles of management

Treatment principles in the management of a patient with delirium focus on the identification and treatment of any underlying disorder, keeping the patient safe and amelioration of symptoms (NICE, 2010). The latter can be subdivided into nonpharmacological strategies and medical management.

Nonpharmacological approaches help keep the patient in touch with reality and therefore less likely to become distressed and agitated:

- Ensure effective communication and reorientation (e.g. explaining where the person is, who he/she is, and what your role is) and provide reassurance for people diagnosed with delirium. Consider involving family, friends, and carers to help with this.
- Managing the environment by avoiding sensory deprivation (e.g. a windowless room) or sensory overload (e.g. noisy environment); ensuring day-night variation in the environment is preserved; providing a large clock; avoiding unnecessary room changes; and trying to have some familiar objects around the patient.
- Maintaining physiological status, e.g. adequate hydration, nutrition, and avoiding hypoxia, constipation.

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- Ensure the patient's safety by anticipating and taking steps to prevent complications such as pressure sores, falls, further infections, constipation, and reduction in mobility.

Pharmacological (medical) interventions aim to reduce symptoms that distress the patient or add to risk. They are targeted at specific symptoms, e.g. pain, psychotic phenomena, agitation. Psychotropic medications should be reserved for older persons in distress or with psychotic symptoms, to prevent them endangering themselves or others. The use of psychotropic medication to manage wandering is *not* advocated.

Short term (<1 week), low-dose antipsychotic medications ('major tranquillizers') are often the pharmacological treatment of choice but are reserved for patients with severe agitation or psychotic symptoms and should be avoided in those with Parkinson's disease and dementia with Lewy bodies. Haloperidol, or olanzapine, are recommended as they have fewer anticholinergic side effects, few active metabolites, and only a small chance of causing sedation and hypotension. For haloperidol, the initial dose should be low, 0.5–1 mg, repeated if necessary, every two to four hours, with careful titration of the dose against symptoms. For patients in whom anti-psychotic drugs are contraindicated, lorazepam 0.5–1 mg orally (which can be given up to two hourly; maximum 3 mg in 24 hours) is an alternative.

Assessment of capacity and best interest decision-making

When a patient has delirium, their cognition will fluctuate. The clinician needs to assess whether the patient has the capacity to consent to treatment. In the UK, the Mental Capacity Act 2005 enshrines in statute current best practice and common-law principles concerning people who lack mental capacity and those who take decisions on their behalf. It sets out a single clear test for assessing whether a person lacks capacity to take a particular decision at a particular time (see section 'Legal and ethical issues in dementia', and also Chapter 58). It is a 'decision-specific' test, in this case whether to accept either treatment for a medical condition underlying delirium or a drug to treat its effects. Everything that is done for or on behalf of a person who lacks capacity must be in that person's *best interests*. The Act provides a checklist of factors that decision-makers must work through in deciding what is in a person's best interests, such as known prior wishes, prior verbal or written statements, and the views of those caring for them.

Referral and liaison

Patients admitted to a care home or hospital should be assessed for their risk of delirium (NICE, 2010). Patients with delirium should, where possible, be treated in their usual environment, but if the cause of the delirium is unknown, if confusion and wandering are not controlled, or if the patient is at risk of developing dehydration, then admission to

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hospital may be needed. Intermediate care may be an alternative if available. This system of care allows for either an increase in nursing care support for patients who are acutely ill but can be managed at home, or a brief admission to a facility that is intermediate between hospital and home, that offers intensive nursing and physiotherapy support, with a view to early discharge home.

Case study 1 An older Person becomes Confused

Mrs S is an 83-year-old lady who lives in a care home and who became confused overnight. She was reported by the staff to be wandering around the corridors in the night. She was reported to be irritable and argumentative when staff tried to get her up and dressed the next morning. The staff member in charge rang the practice to request a home visit for Mrs S. The GP noted that Mrs S has diabetes, treated hypothyroidism, hypertension, osteoarthritis, hiatus hernia, and recurrent urinary tract infections, and her medications are metformin, levothyroxine, ramipril, simvastatin, omeprazole, and paracetamol.

The GP visited Mrs S and established with the care home staff that she had become suddenly unwell the previous evening. Mrs S was reported to have eaten breakfast and was drinking plenty. She had been incontinent of urine, which was unusual for her. On examination, she was disoriented in time and place and more confused than usual. She was reluctant to be examined. She was afebrile and her pulse and BP were stable (compared to usual readings), her chest was clear, and there were no focal neurological signs. The staff had been unable to collect a urine specimen.

A provisional diagnosis of urinary tract infection was made and she was commenced on trimethoprim, with a request made to collect a urine specimen before and after treatment if possible. The GP also took blood for FBC, U&Es, and blood glucose (recent HbA1C and thyroid function tests had been satisfactory), and requested that the staff monitor Mrs S carefully and discussed how to manage the situation should Mrs S wander about during the night. The GP suggested that the staff should contact the practice again if Mrs S did not improve.

The GP also arranged to return to the care home to review the patient and her medication, particularly to discuss the need for simvastatin and regular omeprazole.

Delusions and other psychotic symptoms

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Psychotic symptoms are not uncommon in the older population and prevalence figures in community samples range from 0.2–4.7% (Targum and Abbott, 1999). In nursing homes, prevalence rates from 10% to as high as 63% have been reported (Zayas and Grossberg, 1998).

Among older patients, psychotic symptoms can be seen in a wide range of conditions. The causes and clinical manifestations of the symptoms usually vary with the underlying condition. Psychotic symptoms of acute onset are usually seen in delirium secondary to a medical condition (see Delirium), drug misuse, and drug-induced psychosis (including of prescribed drugs). Chronic and persistent psychotic symptoms may be due to a primary psychotic disorder (chronic schizophrenia, late-onset schizophrenia, delusional disorders, affective disorders), psychosis due to neurodegenerative disorders (Alzheimer's disease, vascular dementia, dementia with Lewy bodies, Parkinson's disease), or chronic medical conditions.

Delusional disorders in older people range from highly circumscribed persecutory delusions, through the presence of both delusions and hallucinations, to a full-blown schizophrenia-like presentation (Table 22.2). Whether these conditions are distinct from schizophrenia is unresolved. Aetiological factors include a genetic component, sensory deprivation (particularly deafness), and long-standing social isolation. Psychotic symptoms can be associated with aggressive or disruptive behaviour (Gilley et al., 1997) and are often a source of distress to caregivers. They can result in neglect and abuse of older patients (Steele et al., 1990) and persistent symptoms often result in admission to a residential or nursing home, which imposes a heavy financial burden (Stern et al., 1997).

Table 22.2 Symptoms of psychosis.

Core symptoms	Delusions, hallucinations
Behavioural changes	Apathy, aimlessness, self-absorbed attitude
Mood symptoms	Depression, anxiety
Vegetative changes	Changes in energy, sleep, appetite
Motor changes	Excitement, posturing, stupor
Cognitive symptoms	Deficits in planning, reasoning, problem solving, working memory

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Psychiatrists refer to 'positive' and 'negative' psychotic symptoms especially in relation to schizophrenia. 'Positive' symptoms refer to the core psychotic features, i.e. delusions and hallucinations, whereas negative symptoms are marked apathy, social withdrawal, and blunting of affect.

Assessment

In principle, the assessment of psychotic symptoms in older people is the same as in younger adults, but there are some nuances; the differential diagnosis, especially where onset is new, should always include consideration of an organic (medical) cause, delirium, side effect of a drug, or an early dementia. Physical conditions can produce psychotic symptoms, e.g. in delirium. Therefore, a thorough medical assessment is required that includes a collateral history from a carer or family member, in addition to a full physical examination to rule out and treat any underlying causative medical pathology. A thorough physical examination and full set of blood tests (to exclude metabolic causes for symptoms) are considered essential. This assessment should be carried out in primary care, the Emergency Department (if a patient has presented acutely and been taken there), on a medical ward (if the patient has been admitted), or by the old age psychiatrist.

Management

It is important to consider whether isolated psychotic symptoms not distressing or adversely affecting the patient require treatment with medication (Kidder, 2003); certainly, if the person is distressed or at risk, pharmacological treatment is required.

As older people are at particular risk of tardive dyskinesia, atypical antipsychotics may be more appropriate, although recent evidence (Douglas and Smeeth, 2008) suggests that the side effects from atypical antipsychotics might have been underestimated, and there is an increased risk of cardiovascular disease, including stroke, and metabolic side effects (impaired glycaemic control and raised cholesterol). A careful assessment of potentially remediable environmental causes such as sensory deprivation, poor lighting, and social isolation improve symptoms. Simple practical measures can reduce stimulations that produce psychotic symptoms, e.g. removing mirrors if reflections cause the delusion of having ghosts in the house, or drawing curtains over windows if the patient has a delusion of being spied upon. Addressing other contributory and causal factors such as physical illness and side effects of medication (particularly benzodiazepines, antiparkinson's drugs, some cardiac drugs, nonsteroidal anti-inflammatory drugs) is equally important. Treatment of older people with schizophrenia can be difficult because of lack of insight and capacity, but response to antipsychotics is usually good (Howard et al., 2018), especially if

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treatment can be prolonged, e.g. by close monitoring or use of depot injections.

The current UK guidance on schizophrenia and psychosis from NICE (2014) addresses the management and treatment of psychotic disorders in adults with onset before the age of 60 years, though clearly many patients will have lived beyond that age. The general principles of management certainly can be applied to the over 60 years age group. The NICE guideline recommends working in partnership with the service user and their carers in an 'atmosphere of hope and optimism' (NICE, 2014). There is a strong emphasis on the management of both mental and physical health, the role and needs of carers, and the recovery model leading to optimal social functioning.

The NICE guidance recommends a prompt referral to mental health services if a distressed person, with an associated decline in social functioning, has transient or attenuated psychotic symptoms, other experiences or behaviour suggestive of possible psychosis, or a first-degree relative with psychosis or schizophrenia. The assessment should be carried out by a consultant psychiatrist or a trained specialist with experience in managing at-risk mental states.

Mental health services should now be offering carers an assessment of their needs forming the basis of an annually reviewed care plan, which should be received by their GPs. Carers should also be advised about their statutory rights to a formal carer's assessment from social care services and how to access it. With the service user's permission, carers are to be included in decision-making and be offered a 'carer-focused education and support programme' (NICE, 2014), which has a positive message about recovery.

Oral antipsychotic medication and psychological input—namely, family intervention and cognitive behavioural therapy—are the mainstays of treatment. Psychological interventions are not recommended on their own.

The management of psychosis in older people requires special consideration not only (and especially) with respect to prescribing medication, but also to the legal framework under which treatment is administered. It is not uncommon for treatment decisions to be made in a patient's best interests under the Mental Capacity Act 2007 when they lack capacity to consent for themselves, for example, when managing behavioural and psychological symptoms in dementia (BPSD), or to use the Mental Health Act 2007 when assessment and treatment are necessary to manage risk to the patient or others.

Referral and liaison

If psychotic symptoms are suspected, an assessment of the risk to the patient (and others) is required, and whether the patient can remain at home. Referral for specialist opinion from old age psychiatry will be

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indicated for new-onset symptoms, the urgency depending on risk, and the availability of family and social support. With the population ageing, more people with psychosis diagnosed in earlier adult life are entering old age and may require ongoing input from specialist services.

Case study 2 A difficult hospital discharge

A patient, Deirdre R, was discharged from hospital to a local nursing home and is newly registered with the practice. Her discharge letter stated that she was admitted to hospital from a residential home with a chest infection and that the previous home refused to take her back because of 'difficult behaviour'. The discharge letter mentioned 'chronic schizophrenia'. Discharge medication was risperidone, temazepam, lansoprazole, ramipril, and bendroflumethiazide.

The day after discharge, the nurse in charge of the home rang the practice and asked for an urgent visit because Deirdre was reported to be aggressive, had urinated in another person's room, and was talking to herself.

The GP agreed to visit Deirdre, but first contacted the hospital ward to ask for further information about Deirdre's usual behaviour. Deirdre had been seen by the old age psychiatry team while she was on the ward and they were arranging follow-up, although it was unclear when this might be. At the visit, the staff complained that they had not been made aware of how difficult they were going to find managing Deirdre and asked if she could be prescribed night sedation. The GP examined Deirdre to ensure that there were no acute physical conditions to account for her increased confusion and arranged for an MSU to be sent.

The GP suggested that a joint visit with the old age psychiatrist might be useful so that her care and management within the care home can be planned, collaboratively with the staff, and arranged for this to be held later in the week. This seemed to be acceptable to the care home staff.

Depression

Depression is projected to be the leading cause of disease burden in middle- and higher-income countries by the year 2030 (Mathers and Loncar, 2006). Depression is a major contributor to burden on the individual, the family, and healthcare costs. Older adults face adversity in areas of ill-health, bereavement, isolation, loneliness, and loss, all of which are associated with depression. The experience of loss is central to

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feelings of anxiety and depression among community-dwelling older people (Kingstone et al., 2017).

Depression in older adults, traditionally defined as age older than 65 years, is associated with disability, increased mortality, poorer outcomes from physical illness, and increased use of primary and secondary care resources (Pearson et al., 1999). Population studies have demonstrated that depression severe enough to warrant intervention is one of the commonest mental health problems facing older people, affecting around one in ten older people in the community (Copeland et al., 1999). Major depression is a recurring disorder and older people are more at risk of recurrence than the younger population (Mitchell and Subramaniam, 2005).

According to WHO data, proportionately more people aged over 65 take their own lives by suicide than any other age group, and most will have suffered from major depression. Older people who attempt suicide are more likely to die than younger people, while, in those who survive, prognosis is worse for older adults (Manthorpe and Iliffe, 2010). A meta-analysis using studies with moderate to high methodological quality showed that the point prevalence of major depression in those over the age of 75 ranged from 4.6–9.3%, whereas rates for sub-threshold depressive symptoms (those failing to reach diagnostic criteria) ranged from 4.5–37.4% (Meeks et al., 2011). Most depressive episodes in late life will be a recurrence rather than a first-ever episode, and the increased women-to-men ratio is in line with that in younger adults. Prevalence rates of depression are increased in brain disorders, including dementia, Parkinson's disease, and stroke, and in people with long-term conditions, e.g. diabetes mellitus, cardiovascular disease (Moussavi et al., 2007).

Why does depression in older people go undetected and under-treated?

Older people consult their primary care practitioner more frequently than younger people, yet depression is diagnosed less often in older people (Chew-Graham et al., 2004). Older people can present with nonspecific symptoms such as malaise, tiredness, and insomnia, rather than disclosing depressive symptoms (Unützer et al., 1999), and these symptoms fit poorly with current classifications of mood disorders. Such classifications have been generated to reflect symptoms observed in younger people and have inherent limitations for diagnosis of depression in older people, whose presentation may differ because of ageing, physical illness, or both (Chew-Graham et al., 2004). In addition, physical symptoms, in particular pain, are common and the primary care clinician may feel they represent organic disease. Similarly, forgetfulness may lead health professionals to be concerned that the patient has cognitive impairment and early dementia, rather than depression (Unützer et al., 1999).

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Older people experiencing or at risk of loneliness may not consider that primary care has a role in alleviating loneliness because it is not an illness (Kharicha et al., 2017). In that study, older people tended to think that primary care practitioners tend to lack understanding of non-physical problems and that a good relationship was necessary to discuss sensitive issues like loneliness.

Older adults may have beliefs that prevent them from seeking help for depression, such as a fear of stigmatization and that antidepressant medication is addictive (Givens et al., 2006), or may not consider themselves candidates for care because of previous experience of help-seeking (Chew-Graham et al., 2012). In addition, older people are reluctant to recognize and name 'depression' as a set of symptoms that legitimizes attending their GP (Chew-Graham et al., 2012), or they may misattribute symptoms of major depression as being due to old age, ill-health, or grief (Burroughs et al., 2006; Overend et al., 2015), and they may use normalizing attributional styles that see depression as a normal consequence of ill health.

Primary care practitioners may lack the necessary consultation skills and confidence to correctly diagnose late-life depression. They may be wary of opening a 'Pandora's box' in time-limited consultations and instead collude with the patient in what has been called 'therapeutic nihilism' (Burroughs et al., 2006). In addition, due to the time-limited nature of primary care consultations, clinical decision-making is often centred around prioritizing competing patient demands that may focus on medical comorbidities. This is especially true in health settings like the NHS where the management of people with long-term conditions is driven by guidelines and treatment algorithms that focus on single diseases. In these time-limited and highly structured environments, competing demands on health professionals' time often lead to prioritization of physical health problems (Rost et al., 2000; Coventry et al., 2011). Additionally, a lack of congruence between patients' and professionals' conceptual language about depression, along with deficits in communication skills on the part of both patients and professionals, can lead to uncertainty about the nature of the problem and reduce opportunities to develop appropriate treatment strategies (Coventry et al., 2011).

Case-finding for depression in older people

Box 22.2 shows the risk factors for depression in older people, identified from large community studies (Colasanti et al., 2010). Thus, case-finding for depression in patients with such risk factors has been advocated using the Whooley questions (Box 22.3) (Whooley et al., 2000), which enquire as to whether over the past month, a person has often: i) felt down or depressed, and ii) experienced little interest or pleasure in doing things. This approach was incentivized under the GMS Contract between 2007 and 2013 to encourage detection of cases of depression.

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Box 22.2 Risk factors for depression in older people

Physical factors

Chronic disease:

Diabetes

Ischaemic heart disease

Heart failure

Chronic obstructive pulmonary disease

Organic brain disease:

Dementia

Parkinson's disease

Cerebrovascular disease

Endocrine/metabolic disorders:

Thyroid disease

Hypercalcaemia

B₁₂ and folate deficiency

Malignancy

Chronic pain and disability

Psychosocial factors

Social isolation

Change in financial circumstances

Being a carer

Change of role and loss of social status

Bereavement and loss

Difficulty in adapting to illness/pain/disability

History of depression

Being in institutional care

Box 22.3 Case-finding questions for depression

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1 During the past month, have you often been bothered by feeling down, depressed, or hopeless?

2 During the past month, have you often been bothered by having little interest or pleasure in doing things?

A 'yes' to either question is considered a positive test.

A 'no' response to both questions makes depression highly unlikely.

Source: data from Whooley, M., Stone, B., and Sogikian, K. (2000). Randomized trial of case-finding for depression in elderly primary care patients. *Journal of General Internal Medicine*, 15, 293-300.

There is some evidence (Arroll et al., 2005) that the further question, 'Is this something you want help with?' increases the usefulness of the screening questions in practice. This may help the flow of the conversation and the negotiation of discussion of distress (Coventry et al., 2011). An assessment of severity of the depression should be made by the GP using a schedule such as Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001). In addition, it is vital that the GP explores with the patient ideas and plans for self-harm, and factors preventing the patient from acting on such ideas or plans.

In terms of screening for depression in later life, the Geriatric Depression Scale (GDS) (Yesavage et al., 1983) is widely used. False positives mean that the use of the GDS in entire practice populations of older people is not justified, but opportunistic screening or screening of at-risk groups may be useful, although there is little evidence to support this. The GDS has the advantage of having a comprehensive website that lists short and long versions in a variety of languages, many of which have cross-cultural validity (Rait et al., 1999). Other authors question the usefulness of such reductionist approaches (Dowrick, 2009) and emphasize the value of professional judgment over the narrow use of schedules (Van Weel et al., 2009).

Symptoms of depression in older people

The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) summarizes the common symptoms often present in depression and which the GP should explore in the consultation; five of more of these should be present for the depression to be classed as major (American Psychiatric Association, 2013). When taking a background history, it is important to identify factors that may precipitate and maintain depression (Box 22.2).

The key symptoms about which the practitioners should enquire include: low mood, reduced interest or pleasure in usual activities, changes in appetite or weight (up or down), too much or too little sleep, poor concentration, fatigue, and feelings of guilt or hopelessness.

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The following nuances are important in older people: somatic preoccupation, hypochondriasis, and the morbid fear of illness, which are more common presentations than the complaint of low mood or sadness. This can cause problems for the GP, as a depressed patient's hypochondriacal complaints can be quite different from the bodily symptoms expected from a knowledge of the patient's medical history. Subjective memory disturbance may be a prominent symptom and lead to a differential diagnosis of dementia, but true cognitive disturbance is also common in late-life depression. This usually takes the form of executive dysfunction, meaning difficulty in initiating and persevering with mental tasks. Anxiety is a common presenting or accompanying symptom and may mask the underlying depression. Dementia may alter the presentation of depression, and primary care clinicians should be aware that sustained irritable disruptive outbursts in patients with dementia may signify co-existent depression. Apathy and withdrawal are not uncommon symptoms and it is thought that apathetic presentations in later life with executive dysfunction may be due to vascular disease of the brain, to which older people are prone. Alcohol misuse is often linked to depression. Lastly, a persistent complaint of loneliness in an older person not usually prone to such remarks, often accompanied by a request to be rehoused, should prompt enquiry into mood, feelings, views on the future, and assessment of risk, and a more systematic enquiry about biological symptoms of depression, along with a formal assessment.

Assessment

Diagnosis is based on clinical interview, observation of the patient's behaviour, and, if possible, a collateral history from relatives and caregivers. The GP should cover five areas in the primary care consultation when depression is suspected in an older person: history, mental state, risk assessment, focused physical examination, and appropriate investigations, including FBC, U&Es, LFT, TFT, vitamin B₁₂ and folate, HbA1C, bone profile, and any further tests dictated by clinical presentation. The risk of self-harm must be established. Even seemingly medically trivial attempts at self-harm in older people cannot be ignored (Manthorpe and Iliffe, 2010) and should be assumed to be due to depression unless proven otherwise. It is important to check carefully for delusional ideas, as assessment and treatment of such patients require early referral for specialist opinion.

Severity of depression can be assessed using a validated assessment schedule such as PHQ-9 (Kroenke et al., 2001) and this is included in the QOF of the GMS contract in England and Wales.

Management of depression in older people

Most patients with depression are managed in primary care settings; however, a substantial number of patients are not recognized, and those who are diagnosed often do not receive effective treatment (Chew-Graham et al., 2004). There is a good evidence base for the management

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of depression in older people (Baldwin et al., 2003). The treatment goals are to treat the whole person, reduce risk, and achieve remission of depressive symptoms (because partial recovery is associated with later risk of relapse and chronicity). A longitudinal primary care cohort study in the Netherlands reported that the median duration of a major depressive episode in late life was 18 months, with two-thirds of patients taking three years to recover (Licht-Strunk et al., 2009).

There are effective treatments for the management of late-life depression (Wilson et al., 2001); however, only one in four depressed older people receive effective pharmacological treatment and fewer than 10% a talking therapy (Singleton et al., 2001; Prina et al., 2014; Pettit et al., 2017), despite the fact that many people express a preference for such treatments (Givens et al., 2006).

It is important that the GP explores the patient's views of their problem and the options that might be available to them. So, for example, a patient's views on antidepressants and talking through treatments or psychosocial interventions, what to expect, and waiting times are vital. In addition, the GP has a role in signposting to third-sector agencies (if acceptable to the patient) and thus should be familiar with groups and local networks in his or her area. Exercise and activity are important. Behavioural activation is a technique that can overcome the withdrawal and apathy that so often exists in late-life depression. It works by helping the patient develop a schedule of activities (which the patient used to enjoy doing but has stopped due to low motivation and apathy), agreed with the patient, with or without a written diary to support implementation. The GP can use some of these techniques within the primary care consultation, particularly advising about diet, exercise, and alcohol, encouraging behaviour change and goal setting, challenging negative thinking, and teaching relaxation techniques. GPs can give self-help leaflets to patients that reinforce the content of their discussion within consultations. Regular follow-up and support are important and is called 'active monitoring' in the NICE guideline for depression (NICE, 2009a).

Psychosocial interventions

Cognitive behavioural therapy (CBT), interpersonal psychotherapy (IPT), problem-solving treatment (PST), and psychodynamic psychotherapy are the most widely researched forms of psychotherapy in later-life depression (Gatz et al., 1998; Pinquart and Sörensen, 2001). In moderate to severe (nonpsychotic) depressive episodes, combining antidepressant medication with a psychological intervention such as CBT or IPT can improve outcomes further (Reynolds et al., 1999).

Behavioural activation has been shown to be an effective treatment for depression (Cuijpers et al., 2007) and results from a 2009 meta-regression analysis suggest that psychological therapy, particularly CBT, IPT, and PST, is equally effective in older and younger adults with

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depression (Cuijpers et al., 2009b). Combined psychological therapy and pharmacological therapy is more effective than psychological treatment alone for older people with depression (Cuijpers et al., 2009a). Anxiety management can be a highly effective adjunctive treatment for depressed patients, especially where patients who are recovering from depression are left with residual anxiety, low confidence, or phobic avoidance, which can undermine functional improvement.

Family work is important: the patient may unconsciously use the family to foster invalidism, which the family may then unwittingly reinforce. The unconscious goal may be to live under the same roof as one's children. More positively, the family is often critical in ensuring a successful outcome in treatment, e.g. reinforcing messages about treatment concordance, exercise and activity, and goal-setting, and the primary care team should work with the family as well as the individual patient.

The UK NHS has invested significant resources to improve access to routine, evidence-based, first-line treatment of common mental health problems for adults of working age by rolling out the Improving Access to Psychological Therapies (IAPT) programme across England. Initial evaluation from the demonstration sites suggested that older people are not referred as readily as those under the age of 65 (Clark et al., 2008).

Stepped care and NICE guidelines

Stepped care for common mental health problems is recommended in the primary mental healthcare setting within the UK (NICE, 2011a). The basic principle of stepped care is that patients presenting with a common mental health disorder will 'step through' progressive levels of treatment as necessary (Bower and Gilbody, 2005). There is limited evidence for this approach, particularly in older people, and it is suggested (Unützer, 2002) that systematic models of care dedicated to proactively managing depression as a chronic illness are required.

Initial management by the GP should include information about depression and referral to third-sector resources such as Age UK. Exercise is recommended by the NICE guidelines as a treatment for mild to moderate depression (NICE, 2009a), but there is only limited evidence for this approach in older people (Singh et al., 1997). Training in the use of the Internet to increase social support has been shown to reduce complaints of loneliness and depression (White et al., 2002) and there is recent evidence that befriending has a useful function in the management of mild depression in older people. Interventions offered need to encourage social engagement, such as befriending, and enhancement of creative, physical, and social activity (Chew-Graham et al., 2012).

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Collaborative care is recommended by NICE (2009a) in step 3 for people with depression and long-term conditions. There is evidence that this approach is effective (Katon et al., 2010). The intervention should involve (Gunn et al., 2006):

- a multiprofessional approach to patient care delivered by a GP and at least one other health professional (e.g. a nurse, psychologist, psychiatrist, or pharmacist);
- a structured patient management plan that facilitates delivery of evidence-based interventions (either pharmacological or nonpharmacological);
- scheduled patient follow-ups on one or more occasion, either face-to-face or by remote communication (e.g. telephone);
- enhanced interprofessional communication between the multiprofessional team who share responsibility for the care of the depressed patient (e.g. team meetings, case conferences, supervision).

A key component of collaborative care is the introduction of a care (or case manager) in primary care. The case manager acts as the conduit between patients and professionals in primary and specialist care and works as the patient's support or advocate to jointly determine problems, set goals and action plans, and offer education and problem-solving skills as ways to promote better patient self-care. The PROSPECT study (PRevention Of Suicide in Primary care Elderly: Collaborative Trial) studied the effect of a depression care manager offering recommendations to GPs according to a guideline and helping patients with adherence to medication (Bogner et al., 2007). The IMPACT study (Improving Mood: Promoting Access to Collaborative care Treatment) utilized a case manager coordinating care and delivering a specific psychosocial intervention (behavioural activation or problem-solving treatment) with or without medication management, and liaising with both the GP and the specialist mental health services (Unützer et al., 2002). Both studies suggest the effectiveness of such a collaborative care approach that has been shown to be acceptable to family physicians (Levine et al., 2005), and evidence from the UK (Chew-Graham et al., 2007; Bosanquet et al., 2017) is promising.

Treatment with antidepressants

Selective serotonin reuptake inhibitors (SSRIs) are well established as first-line treatment for moderate to severe depression in older adults. A Cochrane review included 32 randomized controlled trials of antidepressant treatment in people aged 55 or over and reported that SSRIs and tricyclic antidepressants (TCAs) had similar efficacy, but that TCAs were associated with more side effects and withdrawal from treatment (Mottram et al., 2006). Consideration of a patient's other medication is required when initiating treatment with antidepressants, although an SSRI will usually be first line. If antidepressants are considered, it is vital that the GP explores the patient's views and

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concerns about such medication, and a full discussion about these drugs, the time taken to work, and the possible side effects are covered.

Ongoing support and review from the GP, accompanied by written information, particularly when antidepressants are prescribed, is important. The patient should be warned about common side effects that can occur when tablets are started (such as nausea, fatigue, headache, and increased anxiety), including longer-term side effects (such as reduced libido and weight gain), and doctors should be aware of the risk of GI bleeding (particularly if the patient is taking aspirin) and hyponatraemia. The patient should be warned about the side effects of stopping an antidepressant abruptly and that it is vital to continue the antidepressant for at least nine months (longer if this is an episode of recurrent depression) to achieve remission of symptoms (National Collaborating Centre for Mental Health, 2011). For further details of antidepressant prescribing, see Chapter 39.

The NICE guideline (2009a) suggests that an SSRI should be tried for at least two weeks, possibly up to six weeks in older people, before considering a change in antidepressant. It is appropriate to start at the therapeutic dose of an SSRI for older people (care being taken to ensure there are no drug interactions). An increase in dose can be tried before an alternative SSRI is prescribed. Alternatively, mirtazapine could be prescribed, particularly if the patient has chronic pain or sleep problems. The GP should attempt to tailor the drug to the patient's symptoms. If there is no improvement in depressive symptoms, it is vital that the GP considers comorbidities, concurrent prescribing, alcohol excess, continuing loss and loneliness, or a diagnosis of vascular depression. In addition, risk of suicide should always be assessed.

Referral and liaison

The role of specialist care in the collaborative care model has been described in Stepped care and NICE guidelines. Referral to an old age psychiatrist is necessary if the patient is at risk of self-harm or suicide, or neglect. Referral should also be considered when treatment with two antidepressants and talking treatment has not led to an improvement of the patient's symptoms. At this stage, discussion with and/or referral to an old age psychiatrist is indicated. Treatment resistance may require a second antidepressant or addition of a mood stabilizer, both of which should only be initiated in specialist care, or consideration of electroconvulsive therapy (ECT). Guidance is outlined in the NICE guideline for depression (NICE, 2009a).

Case study 3 An Multimorbidity and depression

Sirfraz Ali consults his GP to discuss the pain in his knees. He is reluctant to take painkillers as he says he is 'already taking so many

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tablets'. He admits that he feels his diabetes has not been well controlled since his wife died, and says he feels lonely even though his grown-up children all live nearby. He is tearful during the consultation and says he feels ashamed of how he feels. He says he is frightened of what his future holds. Sirfraz admits that he feels low but insists that this is understandable as his wife died and he feels a burden on his children. He says that he should be strong and feels angry with himself for being 'like this'. He denies thoughts of harming himself, although admits reluctantly that he wishes every night that he won't wake up in the morning. He has had recent blood tests which confirm a high HbA1C, but all other tests are normal. A PHQ-9 is 18 and the GP suggests that Sirfraz may be depressed. He is not happy to use this word and says that he 'shouldn't have mental problems'. The GP acknowledges his feelings about the word 'depression' and suggests that there are ways of improving how he feels and that he might wish to attend a local support group (the GP is aware of two groups in a local community centre that are for South Asians, and one group in a local church for people with diabetes), but also gives Sirfraz some written information about depression. They discuss things that Sirfraz used to like doing and established that he likes cricket and photography, so the GP asked him to think about how he might get back to these hobbies.

On review two weeks later, Sirfraz is no better; he hadn't felt able to contact the support groups, and said most days he was just sitting at home, was not answering the telephone, and had stopped his family coming around to see him on two occasions. The GP asked if he wished to talk more about how he felt and how this was affecting his life. Sirfraz said that talking wasn't something he felt comfortable with, so the GP suggested that antidepressants might help, and discussed how it is thought they work, how long they would take to work, and what the potential side effects might be. Although reluctant, Sirfraz agreed to take a prescription, but also agreed that he could be referred to the local IAPT (Improving Access to Psychological Services) service, saying that he would be willing to be seen, although he did not want to participate in a group. The GP asked Sirfraz if he would return in a further two weeks. The GP contacted the local IAPT service to see if they had therapists who work with people with long-term conditions (LTCs) and depression, and also talked to the practice nurse about how the practice could better offer support to people with depression and LTCs.

Anxiety

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Epidemiology

Anxiety disorders are more common than depression in all age groups and as common in older people, and are accompanied by significant morbidity; the 2007 UK household survey reported a 9% prevalence of mixed anxiety and depression (McManus et al., 2009). 'Anxiety' covers the terms generalized anxiety disorder (GAD), panic disorder, obsessive-compulsive disorder, and phobia (National Collaborating Centre for Mental Health, 2011). GAD is a common disorder, of which the central feature is excessive worry about different events associated with heightened tension. A formal diagnosis using the DSM-IV classification system requires two major symptoms (excessive anxiety and worry about a number of events and activities, and difficulty controlling the worry) and three or more additional symptoms from a list of six (feeling wound-up, tense, or restless; becoming easily fatigued; concentration problems; irritability; tension in muscles; and difficulty with sleep). Symptoms should be present for at least six months and should cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Symptoms of anxiety

Patients complain of worry, irritability, tension, tiredness, or 'nerves', but older people may complain of somatic symptoms that may cause difficulty for the GP and may result in unnecessary investigations for the patient. Anxiety often co-exists with depression, and the GP also needs to be aware of the link with alcohol misuse and should always explore alcohol consumption in older people who present with symptoms of anxiety.

Assessment

Some clinicians consider anxiety and depression to be part of a continuum, and labelling the patient as having one disorder or the other may be less important than assessing the severity and impact on the patient's life. This may be a valid perspective in primary care, where people often present with mixed or comorbid problems, but it is important to distinguish which symptoms are most prominent in order to focus explanations, identify appropriate management and resources, and ensure referrals are made (Buszewicz and Chew-Graham, 2011). Thus, the use of the GAD-7 has been advocated as a useful instrument to assess severity of anxiety and thus direct management (Spitzer et al., 2006). The need to assess risk to the patient is often overlooked when the predominant symptom is anxiety, but patients are at risk of self-harm and self-neglect, and the GP should be aware of this.

Management of a patient with anxiety

Anxiety and depression are often comorbid conditions. The NICE guideline for anxiety (NICE, 2011c) advocates a stepped care model for the management of people with anxiety and this approach is appropriate for older people with anxiety symptoms, with or without depression. Thus,

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discussion with the patient about the symptoms and their meaning should occur, followed by negotiation of a management plan acceptable to the patient. When physical symptoms are the presenting problem, appropriate physical examination may help to reassure the patient that their symptoms are being taken seriously, but repeated investigations should be avoided. Initial management should involve verbal and written information about anxiety and signposting to age-appropriate support groups (e.g. Age UK) or self-help groups (Anxiety UK), and discussion of behavioural activation techniques, with an arrangement to follow the patient up. This constitutes 'active monitoring' in the NICE guideline for anxiety (NICE, 2011c). As in the management of depression, appropriate advice about alcohol and activity should be given.

If there is no improvement of symptoms, then discussion with the patient about the acceptability of referral for 'low-intensity psychological interventions' should take place. If this is unacceptable to the patient, then the GP should discuss with the patient how the patient would feel about taking antidepressants (SSRIs) and the rationale for this suggestion. Management of anxiety in older people should be no different from management in younger adults (see Chapter 42), although the link with chronic physical health problems means that a collaborative care approach (see Stepped care and NICE guidelines) may be indicated, although there is limited evidence for this and further research is advocated (Buszewicz and Chew-Graham, 2011).

Referral and liaison

Occasionally, patients with GAD suffer severe functional impairment, or are at risk of self-neglect or self-harm (NICE, 2011c). In such cases, urgent referral for a specialist opinion is required. Persistence of symptoms should also lead to discussion with a specialist, and research is required to assess the place of a collaborative care model for the management of people with anxiety.

Case study 4 A frequent attender

Miss Peters is 67 years old and has presented at the desk asking to be seen. The receptionist asks the GP on duty what she should do as Miss Peters seems quite agitated. She informs the GP that Miss Peters has already been seen in the practice once this week, and the GP sees from the computer records that she was complaining of abdominal pain and nausea. Today she is apparently complaining of chest discomfort and shortness of breath. The GP notes she is taking mirtazapine, ramipril, bisoprolol, calcium and vitamin D tablets, and paracetamol.

The GP asks Miss Peters to take a seat in the waiting room and tells her that she will be seen at the end of surgery. Miss Peters is calm

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when she enters the consulting room, but soon becomes agitated and tearful and talks about her constant fear that 'something awful is going to happen'. She is distressed and clutches her chest. The GP establishes that her chest pain is not exertional and does not sound cardiac. The GP reflects to Miss Peters about her repeated attendances and her symptoms and asks her what she thinks might be wrong. Miss Peters insists that she must have a heart problem and thinks she needs to go to hospital.

The GP acknowledges her worries and suggests that there might be other ways of managing her problems and asks her if she would complete a GAD-7. She agrees and scores 16. The GP suggests she might be suffering from anxiety and that there is help available. Miss Peters does not seem sure about this and insists that it is her body that has the problem and she says she has 'nothing to be anxious about'. Initially, the GP gives Miss P some reading material about anxiety and provides a relaxation CD, along with the suggestion that setting herself a goal to achieve each day might be helpful. The GP also mentions referral to the local primary care mental health service and antidepressants as options, and asks Miss P to consider both these before the next appointment, which they arrange in two weeks.

The GP is careful to document this consultation in detail in the records, so that if Miss Peters contacts the practice again before the next scheduled appointment, the consulting GP is aware of the plan negotiated at this consultation.

Dementia

In 2015, there were around 47 million people worldwide living with dementia and this number is projected to triple by 2050 (Livingston et al., 2017). In the UK, about two-thirds of people with dementia live in private households, with the majority of their care provided by primary and community care teams (Prince et al., 2014). With age the strongest risk factor for dementia, the illness is currently one of the major causes of care burden and disability in later life; costs of care are estimated to be around £28 million and rising (Prince et al, 2014). However, recent findings from large epidemiological studies have shown that both the incidence and prevalence rates of people with dementia is almost 20% less than predicted 20 years ago (Matthews et al., 2013; Matthews et al., 2016) despite ageing populations. Thus, numbers of people with dementia will continue to rise but perhaps at a slower rate than was anticipated. This is thought to be due to better vascular risk control and chronic illness care as well as better education.

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As a consequence of these findings, many high-income countries have introduced public health strategies, such as national dementia awareness campaigns, to help improve awareness of dementia and thus facilitate earlier diagnosis. In the UK, a national dementia strategy was introduced in 2009, and since this date, dementia diagnosis rates have increased from less than 40% in 2009 to 67.5% in 2018 (NHS England, 2018).

Symptoms and initial presentation

The diagnosis of dementia can be delayed by the insidiousness of the symptoms and the perceptions of both lay and professional people that these may be due to normal ageing (Bamford et al., 2007). General practice is often the first point of contact for patients with memory problems or other suspicious symptoms. Individual GPs will have different abilities and confidence in diagnosing and managing dementia, although professional confidence in this area appears to be increasing in the last decade (Tang et al., 2018).

Initially, the patient may present with memory problems, communication difficulties, behavioural issues, and/or personality changes; they are often accompanied by a concerned family carer (Bamford et al., 2007). As the illness moves into the moderate stages, memory and communication difficulties worsen and there may be concerns around personal care and/or safety issues, such as non-concordance with treatment in a previously compliant patient, hoarding of medication, missed appointments, difficulty managing money, and poor coping at home. Suspicions of family carers recorded in patients' notes help prompt further evaluation at subsequent contacts, and aid earlier diagnosis (Bamford et al., 2007).

Indirect presentation of a patient with possible dementia to other members of the primary care team or other community professionals is common. Practice receptionists or community pharmacists may report missed appointments, difficulties in patients' management of repeat prescribing, or obvious confusion or distress over medication. The community nurse or social worker may observe disorientation of a patient visited for other needs, or a health visitor may report a family crisis precipitated by failure to cope with a person affected by undiagnosed dementia.

Assessment

The initial assessment should include a careful history from the patient and their main carer, with relevant information from the patient's notes; a physical examination with baseline investigations and an objective cognitive assessment should be also carried out by the GP (NICE, 2018). The first step for the GP is to exclude a potentially treatable illness or reversible cause of the dementia, as in Case study 5. A history of a recent fall suggests the possibility of a subdural haematoma and, if suspected, immediate referral to a geriatrician or neurologist should be made for an urgent CT brain scan. A review of medication may identify incorrect

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dosage or drug interactions that are causing intellectual impairment. These may include sedatives, tranquillizers, antiparkinsonian agents, and hypotensives; adjustment or withdrawal of these will clarify the diagnosis. Normal pressure hydrocephalus, hypothyroidism, syphilis, hypercalcaemia, and vitamin deficiencies as the cause of, rather than result of, dementia are rarities in practice. For GPs, depression masquerading as dementia ('pseudodementia') is probably the most common differential diagnosis and should always be considered; if suspected, a trial of antidepressants may be indicated.

Case study 5 A patient with memory loss

The warden of a sheltered housing unit requested a GP to visit Mrs W, a 78-year-old female resident who had been 'going downhill' mentally for the past few months with memory loss, intermittent confusion, incontinence, and difficulty with self-care. The patient had a past history of atrial fibrillation and transient ischaemic episodes from cerebral emboli, and had been commenced on warfarin. The warden recalled a fall six weeks earlier, after which the patient had been examined at hospital and reassured that no injury had occurred. Rereferral for further investigation resulted in the detection of chronic bilateral subdural haematomas on CT scan, with no cerebral atrophy. Following surgery, her confusion cleared. Despite only partial recovery of memory, she was again able to cope alone.

A physical examination of the patient, particularly to look for anaemia, cardiac disorders, neurological evidence of previous stroke, and undiagnosed malignancy, is essential. Baseline investigations in primary care should include full blood count (FBC), erythrocyte sedimentation rate (ESR), biochemistry, and thyroid function tests, although results are more likely to detect co-existent medical pathology than to aid the differential diagnosis of dementia. The correction of iron- or vitamin-deficient anaemias, the control of cardiac arrhythmias, and treatment of hypothyroidism are good medical practices, but there is a risk of the GP diverting clinical interest into 'medicalization of the patient', rather than confronting the management of the underlying dementia.

Use of cognitive assessment tools in primary care

A number of simple tools are available for use in the community to make an initial assessment of a person's cognitive function; no single brief cognitive assessment tool performs better than any other (NICE, 2018). Until issues with copyright, the most commonly used cognitive assessment tool was the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). It is scored out of 30 with a score of less than 25 being suggestive of dementia. However, this can take up to 20 minutes to

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complete and may not be practical for use within a primary care consultation, which is usually seven to ten minutes in length. The General Practitioner Assessment of Cognition (GPCOG) (Brodaty et al., 2002), and two other cognitive screening tests, the Mini-Cog Assessment Instrument (Borson et al., 2000) and the Memory Impairment Screen (MIS) (Buschke et al., 1999), have been found to be as clinically and psychometrically robust and more appropriate for use in primary care than the MMSE (Milne et al., 2008). The GPCOG is estimated to take five to seven minutes to complete, with questions for both the patient and family carer, and thus may be more relevant for primary care physicians (Brodaty et al., 2002). Another alternative, developed in primary care, is the six-item Cognitive Impairment Test (6CIT), which performs as well as the MMSE and is easier to use (Brooke and Bullock, 1999). Addition of a clock-drawing test may also be a useful quick and simple test for the GP to use (Shulman, 2000).

Specialist assessment and confirmation of the diagnosis

If the GP is highly suspicious of a possible diagnosis of dementia, he/she should refer the patient for a specialist multi-disciplinary assessment preferably to old age psychiatry or, if locally available, a memory clinic (NICE, 2018). Increasingly, old age psychiatry and memory clinics have access to specialist scanning facilities to enable not only a diagnosis of dementia to be made but also a specialist subtype of dementia to be confirmed (NICE, 2018). Case study 6 illustrates the advantages of early referral, including relief at acquiring an explanation for distressing symptoms; access to anticholinesterase inhibitor drugs and specialist cognitive rehabilitation and/or psychological interventions; advice on appropriate information and support services, including day care; carer assessment and support; and the ability to undertake advance care planning (Robinson et al., 2015).

Case study 6 A patient with dementia

George P, a 77-year-old man with a history of hypertension, hyperlipidaemia, and polycythaemia, presented to his GP with concerns about his memory but no disturbance of function. An initial MMSE score was 27/30. The GP arranged to review him at six-monthly intervals. One year later, he attended with his wife who was very concerned. She stated he was becoming confused and disorientated when outside; his MMSE was now 24. He was referred to the memory clinic, where a scan revealed changes consistent with vascular dementia. He and his wife chose to complete a Lasting Power of Attorney for finance and to visit the local dementia café for peer group support.

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If patients are in the moderate to severe stages of the illness, it may be less distressing for them to have an initial specialist assessment in their home in the presence of relatives; this can also facilitate a joint assessment with the local authority social services care coordinator to discuss both diagnosis and a future care plan. Despite the need to inform patients and their families sensitively and accurately of a diagnosis of dementia, disclosure rates vary considerably; often, family carers are told the diagnosis more frequently than patients and that there is still considerable use of euphemistic terms by health professionals (Robinson et al., 2011).

Long-term management in the community

People with dementia live an average of five years from the emergence of symptoms (Rait et al., 2010). Together with their old age psychiatry colleagues and/or community mental health teams, the GP and the primary healthcare team are responsible for coordinating and directing the long-term clinical management of patients with dementia; local authority social services are responsible for the social care and support of the patient (Robinson et al., 2015). Treatment of medical conditions co-existing with dementia should be continued, if supervision is available, until a decision is made for palliative care. Prescribing of cholinesterase inhibitors to people with mild/moderate dementia is recommended (NICE, 2018) in order to slow the rate of deterioration. Shared care protocols provide a framework for GPs to continue prescribing such drugs once a specialist decision to initiate treatment has been made (NICE, 2018).

In the UK, national guidance (NICE, 2018) and the National Dementia Strategy (Department of Health, 2009) both propose a systematic approach to the long-term support of people with dementia in the community, with care plans tailored to the needs and circumstances of individual patients and carers and, more recently, the specific allocation of a named care coordinator (NICE, 2018). Such an approach should include: the provision of psychosocial interventions to help reframe dementia and reduce the rate of cognitive decline; the provision of relevant information on prognosis; care options and financial and legal issues; the recognition of personal and social needs; the assessment and support of key carers (Cameron et al., 2011); the treatment of underlying medical conditions or disability; the management of behavioural problems and relationship difficulties; and ensuring where possible, that the patient remains in their preferred place of care for as long as is feasibly possible (Livingston et al., 2017).

Nonpharmacological interventions for the person with dementia

There is increasing evidence that some non-drug interventions can improve short-term performance or reduce the rate of cognitive decline, especially if combined with anticholinesterase medication (Alzheimer's Disease International, 2011; NICE, 2018). Such interventions include cognitive rehabilitation (a more individualized approach to help people

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focus on residual cognitive skills and improve their coping strategies); cognitive stimulation (an approach that targets cognitive and social functioning through reality orientation and other activities); reminiscence therapy (discussion of past activities, events, and experiences); and occupational therapy. Unfortunately, often due to a shortage of specialist services, such psychological therapies may not be easily and readily accessible to people with dementia, despite their being recommended in national clinical guidance on dementia (NICE, 2018).

Management of behavioural problems in the community

Most people with moderate to severe dementia will experience behavioural and psychological symptoms (BPSD) at some time, particularly in the middle and later stages (Savva et al., 2009). However, while the risks, such as wandering and getting lost, from such behaviour are often not as high as carers fear (Robinson et al., 2007), BPSD can lead to high levels of carer stress or curtailment of the person with dementia's activities, and they may be the crucial factor that leads to care home moves (Balestreri et al., 2000).

National guidance in the UK recommends non-drug approaches as the first-line management of such symptoms (NICE, 2018), but in the community this can be very difficult to achieve due to i) a lack of access to specialist nursing and psychological services to enable an individualized assessment of patients and their environment, to determine the antecedents, behaviours, and possible causes ('ABC' approach); and ii) the limited high quality evidence for the clinical and cost effectiveness of nonpharmacological treatments (NICE, 2018).

The UK has recently developed a multi-disciplinary pathway for the optimized management of BPSD. This pathway provides evidence-based guidance to primary, secondary, and community care professionals, including care home staff, on the holistic management of these challenging behaviours (Alzheimer's Society, 2011). If the behaviour persists and becomes more severe despite the use of non-drug approaches, the GP can prescribe a short course of an antipsychotic drug, such as risperidone (0.5–1mg); however, prescribing of these drugs should be time limited and only reserved for severe and distressing symptoms after careful assessment of the risks and benefits of their use and consideration of the type of dementia (O'Brien, 2008; Burns and Iliffe, 2009). There is some evidence that antidepressants, such as citalopram, may help behavioural symptoms including agitation and psychosis (Pollock et al., 2002). Cholinesterase inhibitors do not seem to be effective (Howard et al., 2007) and stopping them should be considered if a person is agitated.

Providing information in dementia

There is some evidence that information provision to families living with dementia can improve quality of life (Corbett et al., 2011). Family

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members and other supporters should have access to information and advice from sources that are accurate and allow them to address their individual concerns, which may be different to those anticipated by clinicians (Livingston et al., 2017; Wald et al., 2003; van der Roest et al., 2009). Accurate and up-to-date information should be available in primary and secondary care, social care, and voluntary and community settings (Robinson et al., 2015). Voluntary or third sector organizations are a major source of information for people with dementia and their families; in the UK, organizations such as the Alzheimer's Society (<http://www.alzheimers.org.uk>), Age Concern (<http://www.ageuk.org>), and Dementia Services Development Centres offer a wide range of information and practical advice, such as the *10 Helpful Hints* series of books (see <http://dementia.stir.ac.uk>). People with financial problems may find caregiving particularly difficult and may benefit from early signposting to financial or debt advice agencies (Robinson 2015). Welfare benefits provide some financial remuneration for people with a chronic illness and their family carers. The Disability Parking Scheme allows people with severe mobility impairment or their carers to park close to the places they want to reach, and is available also to those with severe memory impairment.

Legal and ethical issues in dementia

The GP is well placed to provide sensitive and timely discussion of legal and financial matters (Robinson et al., 2015), including information and advice about seeking Power of Attorney (POA) and advance care planning (ACP) for future health or care preferences (see Chapter 58). In England, the introduction of the Mental Capacity Act 2005 has provided a statutory framework for acting and making decisions on behalf of adults who lack the mental capacity to do so for themselves. The code of practice associated with the Act provides guidance on good practice for those acting under the terms of the Act. It contains i) guidance on how to assess capacity; ii) a statutory framework for an advance directive; and iii) advice on how to manage patient decisions, once the advance directive is applied (Department of Constitutional Affairs, 2007). The Act has also established an Independent Mental Capacity Advocate (IMCA) service; this provides representation and support for individuals who lack capacity but who have no one else to support them when major decisions are being made about their lives.

The Act has also seen the introduction of a new formal POA, the Lasting Power of Attorney (LPA), which has replaced the provision for existing Enduring Powers of Attorney (EPA), although the latter remain valid if executed before the implementation of the 2005 Act. LPAs extend the areas in which donors can authorize others to make decisions on their behalf to include personal care and medical treatment, i.e. any matter of personal welfare, in addition to LPA for property and financial affairs.

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ACP is a term used to refer to a series of discussions between patients, their families, and care professionals about their future wishes for their care should they lose capacity. There is some evidence that ACP can improve patient and carer outcomes in dementia (Robinson et al., 2012; NICE, 2018). Following these discussions, patients can formally record their wishes in a number of ways, including the completion of an advance directive, or living will, as it was previously known (see Box 22.4). In the UK, NICE (2011b) has provided quality standards on end-of-life care for adults, and there is a current debate about the choices that should be offered to people as they near death.

Box 22.4 Outcomes of advance care planning discussions: International and national terminology

- Statement of wishes and preferences:
 - Documents an individual's wishes and preferences for future care and is not legally binding.
 - In the UK, this is known as an advance statement.
- An advance directive for refusal of treatment (originally known as a 'living will'):
 - Comprises a statement of an individual's refusal to receive specific medical treatment in a predefined potential future situation.
 - It is legally binding and comes into effect when a person loses mental capacity.
 - In the UK, this is known as an advance decision to refuse treatment (ADRT).
- A proxy decision-maker or Power of Attorney (POA):
 - A legally binding document whereby the person nominates another ('attorney') to make decisions on his or her behalf should he/she lose capacity.
 - In England, following the introduction of the Mental Capacity Act, this is now known as a Lasting Power of Attorney (LPA); there are two separate aspects to LPA, one in relation to a person's health and welfare and another in relation to property and affairs.

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Caring for the caregivers: The role of the GP

Carers of people with dementia are more likely to experience depressed mood, to report a higher burden, and to have worse general health compared with carers of people with other long-term conditions (Brodaty et al., 2002; World Alzheimer Report, 2011; see also Chapter 54). In dementia, carers may grieve or experience loss as their relative loses functional and cognitive abilities and the tangible benefits of companionship, affection, and intimacy (Zarit and Zarit, 2008); this experience has been likened to 'coping with a living death' (Woods, 1989). Depressed mood in the carer is one of the factors that determine the move of the person with dementia to residential care (Gallagher et al., 2011) and may lead to abuse of this person with dementia. In view of the evidence, primary care physicians should endeavour to provide proactive carer support and to monitor their health and wellbeing, in addition to caring for the person with dementia (Cameron et al., 2011; NICE, 2018).

There has been a considerable increase in research in the area of specialist multicomponent interventions for family carers of people with dementia, which have been shown positively to influence both carers' health and care home admission rates (NICE, 2018). At a personal level, carers expect realistic information about dementia, the implications of the diagnosis, and its prognosis, and how to make best use of available facilities. Services should be adapted to the individual circumstances of the carer and the patient, and be culturally sensitive to differing racial, cultural, and religious backgrounds. The carer should be accepted as a contributing member of the care team, and effective communication with carers should be encouraged through discussion and the keeping of clear, concise records. For housebound patients, a shared care record, held in the patient's home, will maintain continuity and improve communication between the different professionals involved.

The carer may or may not be registered with the same practice as the patient. Overall, the evidence suggests that clinicians need to tailor interventions to the specific needs of individual carers and systematically assess carer needs (Pinquart and Sörensen, 2006; Sörensen et al., 2006). As it is the family that bears the major burden of caring for older people, the GP is the pivotal support for the family unit. The GP's role should include offering advice to carers on their personal health, acknowledging the carers' crucial contributions and the problems they experience, and giving emotional support by counselling the carer on their attitudes and expectations (Cameron et al., 2011). Vigilance by the GP in detecting early signs of strain or poor coping will help to avert crises; high rates of carer abusive behaviours towards care recipients have been recently reported in the UK (Cooper et al., 2009).

The community nurse team may also have a valuable supporting role, teaching carers the practical skills needed for home nursing and providing emotional support.

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Some areas of England have access to an Admiral Nursing Service; these are specialist nurses with expertise in dementia care and, in particular, carer support (Bunn, 2013). However, to date, evidence shows little difference in patient or carer outcomes between families receiving this specialist service and those supported by existing community teams (Woods et al., 2003). Although respite or short-break care is often offered as a means of providing support to the carer, and is positively received by them, the long-term benefits remain unclear (Mason et al., 2007).

Ensuring preferred place of care and care at home

The success of maintaining the patient at home depends on the carer's reason for caring, the quality of the relationship with carers, and identifying and addressing the carers' needs. Regular visits by the community psychiatric nurse, the community nurse, and a named GP, regardless of whether the patient lives alone or with carers, provides support and a coordinated, multi-disciplinary approach between primary and secondary care. Support services from local authority social services can include home care assistants, delivery of ready prepared meals, advice on financial benefits, and respite care. In the UK, voluntary organizations such as Age UK and the Alzheimer's Society can provide a wide range of support, including information and advice (legal and financial) as well as practical support via peer support groups, dementia cafes, carer support groups, sitting services, and respite care.

In addition to behavioural disturbances, other distressing problems arise with the progression of dementia and include sleep disturbance, swallowing difficulties, food and drink refusal, incontinence, and immobility. Advice can be offered on regular toileting to encourage continence and, if incontinence is a problem, aids such as pads, pants, and protective mattress sheets are available through the community nursing services. Referral to appropriate allied health professionals, such as the community physiotherapist, speech therapist, and occupational therapist, for their specialist assessment should be considered to enhance a patient's functional health and also facilitate access to aids and adaptation to help the family cope at home.

The patient with dementia who lives alone

Providing primary care services for older, demented patients who live alone poses special problems, and may only be possible through the goodwill of neighbours and external social care support. If access to the home is unreliable, arrangements should be made with neighbours to hold emergency keys. Neighbours are reassured by contact with the GP and by discussion about when to request help. If there is no available supervision from family carers or the community nurse team, the taking of medication can be simplified by use of a dosette box in which medication is placed into daily dosage compartments dispensed on a weekly basis by a pharmacist. Single patients with dementia may cause concern over security, and personal road and home safety. The local

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police welcome information about these vulnerable residents and this is particularly encouraged if there is a local neighbourhood security scheme. When eventually these patients require admission to a protected environment, a residential care or nursing care home is more appropriate than a sheltered housing unit, where the need to become familiar with new surroundings whilst still living independently is liable to accentuate confusion, as illustrated in Case study 7.

Case study 7 A Person with Dementia who Lives Alone

An 84-year-old woman with dementia who had no relatives lived alone with difficulty. The social services arranged admission to a nearby sheltered housing unit. Within a short time, she appeared more confused, her room became squalid, and she roamed the streets and was frequently returned by the police. She developed paranoid behaviour, attacked several residents, and was formally admitted to hospital under Section 2 of the Mental Health Act. Following assessment and treatment, she was stable enough to be transferred to a nursing home for people with dementia.

Social care for people with mental health problems

Social care covers a range of services and support to help people maintain their health and independence in the community (see also Chapter 25). Such services include home care (personal care, meals, laundry, shopping), day services, respite care, and, if available, residential and/or nursing care. In the UK, recent policy and legislation has aimed to improve the current provision of community care through increasing the choices available to users of these services and creating more integrated services. Initiatives include the inclusion of a Personal Health and Social Care plan in a patient's records to integrate health and social care provision, the establishment of joint health and social care teams, and the introduction of personal budgets, whereby people who require social care can opt to receive payments directly and purchase services themselves, potentially enabling greater choice and control. Evidence has revealed that personal budgets have the potential to achieve greater efficiency while giving people greater control and satisfaction (Alakeson, 2007; Carr, 2010). In dementia care, social care also has a safeguarding role in terms of the increased vulnerability of people who may not have the mental capacity to make their own decisions. There is increasing support for integrated health and social care models as a means of providing more integrated and person-centred dementia care (NICE, 2018).

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Respite care

Carers are at risk of increasing isolation and exhaustion through the intensity of their 24-hour responsibilities. To prevent this, and to delay institutionalization, the GP should emphasize the value of relief care, which can be organized on a daily basis, through day centres or sitting services, or on a longer-term basis through rotation of care with other family members, or planned regular admissions to respite beds in residential care or hospitals. The GP should be prepared to advise carers and families on respite care, and offer information on the range of options and the referral process appropriate to the patient's level of dependency.

For support in the home, domiciliary care may be offered by voluntary organizations or home care agencies such as Age UK, the Alzheimer's Society, and local authority social services. Families and carers are reassured to know that voluntary organizations are regulated and required to work to specific care standards. Short-term care can be arranged in residential care homes for patients who are mobile and only mildly confused; short-term care in nursing homes or hospitals should be arranged if the patient needs more intensive nursing care, is seriously confused, or doubly incontinent. If the patient is self-funding, private care arrangements are made, but if financial assistance is needed, referral for a community care assessment should be made to the local authority social services by the carer or GP well before the planned admission date (see Chapter 26). Patients are assessed against eligibility criteria for funded care. When a patient requires nursing care or supervision, or needs multi-disciplinary assessment and rehabilitation, admission to hospital or a nursing home is the responsibility of the NHS. Since April 2004, the NHS and local authority councils have been required to identify people who are likely to require short-stay respite care, and to agree arrangements for their management.

Although respite admission provides an opportunity for multi-disciplinary assessment of the patient, and may delay institutionalization, it may not reduce the overall burden on the carer. Heavily dependent patients may need regular admissions, e.g. for two out of every eight weeks, to ease the strain on carers. Relatives appreciate the opportunity of visiting the home or hospital beforehand to gain confidence in the staff and the surroundings, as the family may have reservations about delegating care to staff who are less familiar with the patient's condition than they are. Disadvantages of respite care for the carer include the difficulties of visiting patients in hospital or nursing homes, feelings of sadness, loneliness, and guilt on being separated from their relative, and the possibility of institutional cross infections. Some carers, however, refuse offers of help or indeed any support; others may stoically underplay the strain of caring, and deny the seriousness of the illness in their relative.

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Situations requiring hospital admission

A point may be reached when the carer is no longer willing, or able, to cope. Increasing disability of the patient outstrips the tolerance of the carer and is particularly likely to occur when sleep disturbance, wandering, incontinence, and immobility are problems. The patient then requires long-term care. It is important to be aware of the abuse of older people, which may be a symptom of strain in the carer (see Chapter 55). If this is suspected, the GP should refer the patient to social services for an assessment, and perhaps for transfer to a place of safety in hospital or residential care.

Acute admissions mostly occur when there is unexpected illness in the carer, or when a mildly demented patient who lives alone suffers a self-limiting illness that, under normal circumstances, would not require admission. In some areas, local schemes such as 'Hospital at Home' initiatives and rapid response nursing teams are available; these provide comprehensive 24-hour nursing at home for people who would traditionally have been cared for in hospital. Out-of-hours emergency calls by relatives who infrequently visit a mildly demented patient living alone, and insist that 'something must be done' before their return home, is not an uncommon crisis, and may express their own guilt.

It is vitally important to provide adequate and timely information between hospital staff and primary care teams involved in caring for older people with dementia or other mental health conditions, as their needs are often multiple and complex. In the UK, the current dementia commissioning guidance for GPs recommends that they are immediately notified of the diagnosis to improve communication and allow the GP to provide immediate support and further discussion with the family (Department of Health, 2011). However, the reality of the situation in practice is somewhat different and GPs may not be aware that a diagnosis has been made until they receive a clinic letter.

For older people with mental health issues who have been admitted to hospital, prompt discharge letters should include information on the patient's care needs, particularly in relation to community services and carer support, medication, general condition, and follow-up requirements. Sending discharge letters with patients to be handed to the GP is unreliable, especially when patients have poor mobility, live alone, or suffer memory loss. First attendances, hospital discharges, and a change in the treatment or condition of a patient should be reported, as should annual progress of patients attending for long-term care. Letters should summarize the findings at consultation, an assessment and management plan, and have educational value for the GP.

When patients are discharged or managed in outpatients, effective liaison between hospital staff and GPs is essential, especially when patient medication is initiated or changed; the consultant should give the GP timely notification of the patient's diagnosis and details of the drug

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therapy. The doctor who signs the prescription has legal responsibility for the consequences of drug treatment, and must not prescribe without adequate clinical information; it is therefore unacceptable for hospital staff to expect GPs to do so. For patients under consultant supervision, medication should normally be prescribed in hospital and dispensed in the hospital pharmacy for not less than 14 days at discharge, or after initiating treatment in outpatients, to ensure they have enough medication.

Intermediate care

The development of rehabilitation and care schemes that are intermediate between acute hospital care and long-term institutional care has led to a range of alternative provision termed *intermediate care*. Such services are designed to maximize independence and prevent unnecessary hospital admissions. Most schemes offer short-term interventions (one to six weeks) and involve cooperative working with other agencies including primary care teams, local authority social services, and the voluntary and private sectors. For acute care, recent developments aim to bridge the divide between hospital trusts and local authorities. Examples include innovative services such as 'hospital at home' or 'supported discharge' schemes in which the patient is discharged early from hospital and supported by intensive home nursing; these are acceptable to both patients and carers and provide care as effectively as hospital admission (Wilson et al., 1999). However, the cost effectiveness of intermediate care schemes in general remains uncertain and the availability of hospital at home schemes is variable (Robinson, 2014).

An alternative to acute hospital admission is the use of small community hospitals or nursing homes, in which inpatient care is provided by GPs and their multi-disciplinary teams who usually have recourse to specialist advice. This is a useful option when insufficient home care or community support makes continuing home care untenable, particularly when mentally impaired patients require acute generalist care or rehabilitation. Continuing care schemes, rehabilitation, and palliative care may be provided by community outreach teams, or by domiciliary and outpatient therapy services as alternatives to day hospital or inpatient care.

Home care services and residential care

Home care provision by local authority social services and independent voluntary sector organizations has allowed people to remain in their own homes for longer than was previously possible before admission to a residential care home or nursing care facility. Intensive home care services and increased contact hours by care staff have contributed to improvements in the quality of life and independence of older people (NHS Health and Social Care Information Centre, 2006). The GP has a coordinating role and acts as a point of contact for community care staff. The decision to transfer a patient into residential care is difficult and

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should only be taken after all possible community support services in the home have been explored with the patient's relatives and the community planning team. The latter consists of community nurses, social services, and, in patients with complex needs, the community matron employed by the local primary care team. Patients or their relatives seeking admission to a home are advised to discuss the situation with the community nurses caring for the patient and with the patient's GP before requesting assessment for a nursing home placement.

Nursing homes lie predominantly within the independent sector and are subject to registration with the NHS (see Chapter 26). Medical care in nursing homes may be provided by an attending medical officer appointed by the home, or more usually by a local general practice under contract for the provision of general medical care. Patients in residential care homes register with a local GP and have access to general medical care in the same way as the general population. Studies have shown that, in the population living in residential care, there is a high prevalence of physical dependency and depression (McDougall et al., 2007; Seitz et al., 2010) and even higher prevalence rates for dementia (Matthews et al., 2013). This results in high rates of consultation, prescribing, and referral for the attending GP, with the workload for patients in nursing homes being double that for other patients over the age of 74 years (Carlisle, 1999).

Managing people with terminal illness at home

In England, dementia is now the leading cause of death in older women. In the UK, over 40% of people with dementia die in the community; however, around one-third of people with dementia die in acute hospitals (Houttekier et al., 2010; Public Health England, 2018). It is the GP who coordinates their care, both for those who die at home and, in the time preceding admission, for those who die in hospital or hospice care. About 70% of older people with dementia die from bronchopneumonia, a finding confirmed on post-mortem (Burns et al., 1990), while cardiovascular disease, pulmonary embolus, septicaemia, and renal failure account for the remainder of deaths.

Prognostic tools have been developed for use in dementia but there is little evidence for their effectiveness or that they change key outcomes such as comfort (van der Steen et al., 2011). Although evidence is limited, there is general consensus that a palliative care approach is appropriate in dementia (NICE, 2018) and best practice recommendations have been made (van der Steen et al., 2014). The principles of maximizing comfort and quality of life should therefore take precedence and the benefits of potentially unnecessary interventions carefully considered. When patients with dementia become ill with a respiratory infection, the GP should discuss the poor prognosis with relatives and discover their preferences and their knowledge of their relative's wishes for the preferred place of care. Wherever the patient is cared for and whatever the mental status, the principles of good terminal care apply (NICE, 2018). These include:

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mouth care; the control of distressing symptoms such as pain and constipation; the involvement of community nurses and specialist palliative care services; and attention to the need for emotional, practical, and spiritual support for both patients and their families.

People with dementia and their families require more input from healthcare and social services prior to death than do people with terminal cancer (McCarthy et al., 1997). More recently, a variety of interventions and new service models to improve the quality of end-of-life care in dementia have been developed and evaluated; however, most studies to date have been small scale (Livingston et al., 2017). In some countries, assisted dying for people with dementia is legally permissible but in others this approach still raises considerable ethical and legal issues (Livingston et al., 2017).

Primary care: Opportunities for research in older people's mental health

General practice provides a wealth of opportunities for research in the area of older people's mental health. To achieve a whole-population approach in epidemiological surveys or in studies of community care-based interventions, it is worth considering the potential of general practice; a successful example is the Cognitive Function and Ageing Study (CFAS), which has recruited a cohort of 13,000 people aged 65 years and over to explore their cognitive, physical, and psychological health (Matthews et al., 2013; Matthews et al., 2016). Advantages of recruitment of patients from primary care include: the possibility of a more accurate database compared to the electoral register; a personal approach to the patient through the GP, which may lead to higher response rates; access to the patient's medical records and up-to-date chronic disease registers; and the GP's personal knowledge and contact with patients, which facilitates data collection and interpretation of results.

The question of whether to involve multiple small practices or one large group practice should be considered, along with the demographic balance of the practice populations; this avoids the use of skewed population samples and ensures the recruitment of sufficient patient numbers. In the UK, the introduction of national research networks, including for primary care, dementia and mental health, within the National Institute of Health Research (NIHR), has been successful in facilitating primary care-based research.

Having enlisted the cooperation of an interested general practice, it is essential to gain consent from participating GPs and, at the outset, to visit the practice to explain the project to all staff. The acceptability of protocols, letters, questionnaires, and pilot studies should be confirmed with staff, before seeking approval from a local research ethics committee. Establishing a link with a key practice administrator and a GP from each practice facilitates effective organization. It is recommended

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practice, according to the requirements of the Data Protection Act 2018, that researchers should obtain the consent of the patients or subjects before the practice is able to release their contact details to the research team.

In communicating with patients, it is essential to provide information on the research project and its potential benefits. The identity of the research clinician and his/her relationship with the practice should be explained. Patients appreciate a choice of venue for an interview, and usually the preferences range between home, the surgery, and the hospital. The researcher should provide a photo identity card, a letter of introduction from the link GP, and a contact telephone number, for security reasons and to reassure patients, relatives, and neighbours. Where door-to-door surveys are being carried out, it is essential to inform the local police, because neighbours will rightly be highly suspicious. There is usually a long lead-in time when setting up research and the actual interviewing, so a check on a patient's health status should be made by practice staff prior to visiting so as to avoid the distress of including acutely ill or recently deceased subjects. A common problem when interviewing in the community is how to respond to patients' requests for medical advice. As the interviewer is not providing general medical care, any difficulties with the patient's consent should be referred to the patient's doctor.

On completion of the research, feedback to the general practices involved helps to integrate the results with the clinical needs of patients, and to foster a sense of purpose and satisfaction. It is courteous to acknowledge the contributions of participating practices in papers submitted for publication. Indeed, if a GP has personally collected research data, joint authorship should be considered. This will provide a sense of goodwill that may lead to further fruitful collaboration with general practice.

Conclusion

Recognition by the primary care physician or GP of early changes, use of clinical intuition, and acting on family worries are vital in the earlier detection of mental health problems in older people. An awareness of the increased risk of depression in older people with comorbid physical conditions is vital. Members of the primary care team should provide holistic care for older people with mental health problems, and their carers, both at the point of diagnosis and in the longer term. Appropriate referral to secondary care and good liaison and collaboration between primary and secondary care are vital in the management of older people with mental health problems. Knowledge of third-sector services and appropriate referral can improve the support available to older people and their carers.

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Memory assessment services

Chapter: Memory assessment services

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Of clinics and services

Memory clinics were first established in the US in the 1970s in specialist centres interested in research into Alzheimer's disease (AD) and dementia. These clinics offered outpatient diagnostic, treatment, and advice services for people concerned about their memory. In addition to general research into dementia, Fraser (1992), describing these early services, identified four core functions:

1. To forestall deterioration in dementia by early diagnosis and treatment
2. To identify and treat disorders other than dementia that might be contributing to the patient's problems
3. To evaluate new therapeutic agents in the treatment of dementia
4. To reassure people who are worried that they might be losing their memory, when no morbid deficits are found.

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The thing that set these memory clinics apart from normal neurological, neuropsychiatric, and old age psychiatric clinics was their specific focus on dementia. None was a full-time operation; most were exactly what they said they were—a clinic, a room in a specific hospital where once or twice a week or month there was a specific focus. The term ‘memory’ seems to have been used in order to avoid the negative connotations of the word ‘dementia’ and to denote a broader interest in cognition. The first memory clinic in the UK was probably that opened at St Pancras Hospital in London in 1983. The numbers of such clinics grew, so that it was possible to identify 20 clinics in 1995 (Wright et al., 1995), 102 in 2002 (Lindesay et al., 2002), and an estimated 222 in 2014 (Hodge and Hailey, 2015), with the orientation of these clinics moving from being research bases to ways of providing a diagnostic service for dementia.

The term ‘memory service’ appears to have first been used in naming the Croydon Memory Service (Banerjee et al., 2007), when SB, together with David Matthews, the team’s leader, coined the term to describe a new team, working out of a dilapidated 1970s psychiatric day hospital in the grounds of the former Croydon Workhouse. Our intentions were twofold when using the term in drafting the National Dementia Strategy (NDS) for England. First, we wanted to indicate that this should be a service whose job was to *serve* people with dementia and their carers, rather than a clinic organized for the convenience of service providers to meet their interests and needs (e.g. to recruit research participants or to be something fun to do on a Tuesday afternoon). Second, we wanted to stress that such services were not about ‘the clinic’ itself, but were instead about what they did (for people with dementia and their carers) —‘the service’.

This chapter is not about how to run a memory service or what tests to use. This book is full of information on how best diagnoses can be made and what constitutes best treatment and care. Instead, this chapter is about how such knowledge can become action that is of use to all those who would benefit from help: how we can deliver care to those with dementia that need it.

So, here we consider who memory services are for and what they should aim to achieve. We consider the evidence base and discuss ‘what good looks like’. But, before considering what we need to do, we need to understand the specific problem that such services are designed to address. We therefore first refresh the rationale for considering the establishment of such services.

Diagnosis rates for dementia

The numbers of people diagnosed with dementia and the proportion of those with dementia diagnosed in the UK has doubled to around two-thirds in the ten years since the publication of the National Dementia Strategy for England (<http://archive.today/spuZP>, Donegan et al., 2017); this has been achieved partly by better coding, but also by real increases

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in the numbers and scope of memory services. This progress is very positive but there is still a way to go. Worldwide, underdiagnosis and late diagnosis remain a major issue. The World Alzheimer's Report 2011 (Alzheimer's Disease International (ADI), 2011) concludes that most people in the world with dementia have not received a formal diagnosis. In most high-income countries, between 20 and 50% of dementia cases are recognized. This 'treatment gap' is even greater in low- and middle-income countries, with 90% unidentified in India. If these data are extrapolated worldwide, 28 million (78%) of the 36 million people with dementia have not received a diagnosis, and therefore do not have access to treatment, care, and organized support that a formal diagnosis can facilitate.

By diagnosing people late or not at all, opportunities for harm prevention at an individual and a societal level are missed. We consider the potential benefits of diagnosis and early diagnosis in more detail below; however, in summary, if dementia is diagnosed, then at the very least people with dementia and their family carers have the possibility of planning for their future and availing themselves of the help, support, and treatments (social and psychological, as well as pharmacological) that are available.

Early and/or timely diagnosis

It is remarkable, but there are still some who would wish to deny people with dementia an early and accurate diagnosis. This case is often made on the basis of an asserted lack of evidence or the lack of a disease-modifying treatment, rather than evidence of disbenefit. There are important principles, including that a diagnosis should never be forced on any family, and that it is reasonable for people with dementia to make a positive decision about when, if ever, they know. However, no one would advocate this sort of therapeutic nihilism in cancer, heart disease, or HIV/AIDS, and nobody should do so in dementia. ADI, in their 2011 World Alzheimer Report, reviewed in detail all the data available and generated a categorization of the rationale for early diagnosis into nine broad themes (Box 23.1).

Box 23.1 World Alzheimer Report 2011: Nine reasons for early identification and treatment of dementia

- 1 Optimizing current medical management
- 2 Relief gained from better understanding of symptoms
- 3 Maximizing decision-making autonomy
- 4 Access to services
- 5 Risk reduction
- 6 Planning for the future
- 7 Improving clinical outcomes
- 8 Avoiding or reducing future costs
- 9 Diagnosis as a human right

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Reproduced from Alzheimer's Disease International (2011). World Alzheimer Report 2011.

This categorization is useful, and is worth reproducing; each element is considered briefly in order to articulate the points made. The statements italicized are those of the authors.

1. Optimizing current medical management— *It's bad medicine not to.* The diagnostic process allows for the identification of potentially treatable or reversible disorders, including infections, depression, medication side effects, and nutritional deficiencies. The diagnosis allows physicians to adjust treatment plans for other health conditions, including avoiding drugs with anticholinergic effects, and to factor in comprehension and compliance challenges. Cognitive health can be maximized by control of behavioural and psychological symptoms, vascular risk factors, nutrition, and social activity.

2. Relief gained from better understanding of symptoms— *On balance, it's better to know than not.* If we ourselves are to have any chance of managing any problem, we need to know what is going on. People with early dementia very often know something is going on but do not know what, and that is a powerful source of strain. Early diagnosis enables people with dementia and their families to understand and adapt to cognitive and behavioural changes in dementia, reducing blame and impatience. Thus, harm is reduced by knowledge. Knowing the causes of problems can resolve anxiety felt by people with dementia and their families.

3. Maximizing decision-making autonomy— *I need to know to decide what to do.* Early diagnosis and early intervention enable people with dementia and their families to plan their finances, lives, and care in the future by identifying the condition at a time when the person with dementia can fully participate in medical, legal, and financial decisions and make plans for future care.

4. Access to services— *without diagnosis I can't get any sort of treatment for dementia.* If you don't know you have it, you can't get the treatments for it. Early diagnosis allows access to treatments, programmes of care, and services for dementia.

5. Risk reduction— *Diagnosis allows for the prevention of harm.* We can act to make the person with dementia, their carers, and the world safer. Dementia places older adults at risk for relationship problems, delirium, motor vehicle accidents, medication errors, and financial difficulties and exploitation, just for a start. Knowing creates time to address safety issues before accidents or emergencies occur. Again, we are preventing harm.

6. Planning for the future— *I need to know to plan.* The early recognition and detection of dementia enables people with dementia, their families, and clinicians to plan more effectively for the future,

including withdrawing from work if still at work and ensuring child safety.

7. Improving clinical outcomes—*Everyone, me, carers, society, does better if I know.* Early diagnosis enables early intervention; early intervention enables improved outcomes for people with dementia and their family carers. Data suggest that interventions, be they drugs, psychological, social, or educational, are of most benefit if given early in the disease process (NICE/SCIE, 2007).

8. Avoiding or reducing future costs—*Early diagnosis delivers better value, saving money.* The driver of long-run costs in dementia is time spent as a resident of a care home, with acute hospital bed days determining medium-run costs. The data reviewed suggest that interventions aimed at people with dementia and also their carers can reduce total care expenditure by preventing acute hospital admission and delaying the time to care home admission. Better outcomes and lower cost equate to better value. This is the fundamental golden equation in health services development, and evaluation and early diagnosis and intervention delivers this.

9. Diagnosis as a human right—*Whose diagnosis is it anyway?* It is still possible to talk to clinicians, who do not specialize in dementia, who will aver that ‘it is better not to know the diagnosis of dementia than it is to be told’. What is striking is how very little support there is for such paternalism and unwanted protectionism. This is a shield that people with dementia and their families neither need nor want. In many cases, this unintentionally toxic position is a reaction in those clinicians of their being uncomfortable in making the diagnosis and communicating it to their patients. The last 25 years have seen increasing attention being paid to ensuring that people with dementia are treated as autonomous individuals with their rights respected. The Fairhill Guidelines (Post and Whitehouse, 1995) stated, ‘because individuals have a right to control their own lives, and because true control depends on knowing about oneself, individuals have a right to full disclosure regarding a dementia diagnosis’. This is a fundamental truth, and the medical profession needs to deal with it and design systems to enable it. A moment spent putting oneself in the position of a person with dementia makes this clear.

In recent years there has been a growing preference for the use of the term ‘timely’ rather than ‘early’ to describe when diagnoses should be made. The INTERDEM group (De Lepeleire et al., 2008) defined timely diagnosis as:

... the time when the patient or caregiver *and* the primary care physician recognize that a dementia syndrome may be developing. The preference for timely diagnosis implies that methodologies should concentrate not on population screening, but on speedy response to the first reported signs of changed behaviour and functioning in the patient.

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Others have highlighted that timely diagnosis incorporates the needs of the patient about when they should receive the diagnosis (Dhedhi et al., 2014). As such, this minor semantic change appears to be preferable for many, as it removes the chronological emphasis of an *early* diagnosis. It also raises an important issue about choice, and irrespective of the benefits of an early and timely diagnosis, there should always be a choice for the patients.

Timely diagnosis and intervention in dementia—an established health policy priority

Responding to this, early diagnosis and early intervention have consistently emerged as key policy priorities in the recent series of National Dementia Strategies. The fourth objective of the French *Plan Alzheimer* was ‘improving access to diagnosis and care pathways’. In the US, early diagnosis of AD is one of the six main purposes of the US National Alzheimer’s Project Act (NAPA), which was passed with bipartisan support and signed into law by President Obama in January 2011. The Secretary of State for Health for England, launching the country’s first NDS (Department of Health, 2008), said:

Current best estimates are that only one-third of people with dementia ever receive a diagnosis of their illness. We can’t hope to address their needs fully, or those of their carers, without a diagnosis being made, appropriate information being given and effective intervention at an early stage. Some have argued in the past that it is best not to let people know. We have long accepted that this should not occur with cancer sufferers. The same should be true for those with dementia. This was one of the most consistent messages emerging from the consultation process from people with dementia.

There are now more than 30 countries with National Dementia Plans listed on the ADI website and all have a focus on early or timely diagnosis. Internationally the World Health Organization’s (WHO) Global Action Plan on the public health response to dementia (WHO, 2017) both have timely diagnosis feature as being a key priority globally.

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What is a memory service?

As discussed, there is a lack of clarity of definition of what constitutes a memory assessment service, a memory service, or a memory clinic. In line with this, previous efforts to group memory services based on their characteristics have failed due to variability in the structure and the process characteristics (Chrysanthaki et al., 2017). What they all share is an interest and skill in the diagnosis of dementia and particularly in the early diagnosis of dementia. A simple statement of what a memory service is for (i.e. its primary aim) is that given in the NDS for England, namely 'Good-quality early diagnosis and intervention for all'; this requires the service to do three things:

1. to provide a good quality diagnosis early in the illness
2. to provide good quality early intervention in dementia
3. to provide this good quality service to all who might need it in a given population.

So, a service without the skills to identify the illness causing dementia (e.g. AD, vascular dementia, Lewy-Body dementia, etc.) and to have a high degree of clinical certainty both in assigning and excluding a dementia diagnosis, would not meet these criteria. Equally, the service needs to have the skill to identify that small group where there is real clinical uncertainty, even after a full multifaceted, multi-disciplinary assessment, and where a longitudinal approach to diagnosis is needed. Using these tests, a service that provides diagnosis but not treatment would also be seen to fail. The issues of what we do to make a diagnosis well and the effectiveness of intervention in terms of clinical outcomes are covered elsewhere in this book and are not considered further here.

Finally, there is the stipulation that the service should work for all in a population. This is based on equity and access; these should not be services for the lucky few, as many memory clinics have been in the past. They need to have the capacity to deal with all incident cases in the area they serve. An average UK Clinical Commissioning Group (CCG) population has 50,000 older people; this means that the service needs to be able to see around 1000 people a year. This would not be possible with the traditional once-a-week memory clinic that sees a couple of new cases per week. We need to have a grander and broader ambition for our memory services.

Memory services can be powerful local agents and engines for change. They are there to empower people with dementia and their carers by providing them with the benefits that come from good quality early diagnosis and treatment. They are also there to enable the whole health and social care system to work well for dementia. Memory services are therefore at the heart of a win-win-win scenario, where there is quality and value improvement for people with dementia and carers, for health services, and for social services.

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More detail is given in the NDS of what a memory service would be expected to do. The full text of its objective 2 reads:

Objective 2: Good-quality early diagnosis and intervention for all. All people with dementia to have access to a pathway of care that delivers: a rapid and competent specialist assessment; an accurate diagnosis sensitively communicated to the person with dementia and their carers; and treatment, care and support provided as needed following diagnosis. The system needs to have the capacity to see all new cases of dementia in the area.

This partial operationalization gives us further information on what such services would be expected to do in order to be considered of 'good quality'. This requires:

- a rapid assessment
- a competent specialist assessment
- an accurate diagnosis to have been made
- the communication of the diagnosis in a sensitive manner to the person with dementia and their carer
- provision of treatment, care, and support needed following the diagnosis
- to do this for all incident cases in the area served.

Such functions have informed the creation of standards such as those set by the UK Royal College of Psychiatrist's Memory Services National Accreditation Programme (MSNAP; <http://archive.today/DonQ8>). These acknowledge that 'memory services differ widely in their organisation, funding, staffing and levels of service, even within the same Trust.' They therefore centre on 'function', rather than any particular model of service delivery, covering:

- Management systems for the service
- Resources available to support assessment and diagnosis
- Assessment and diagnosis
- Pharmacological interventions
- Signposting to ongoing care management and follow up
- Psychosocial interventions

Communicating the diagnosis well

Communicating the diagnosis to people with dementia and their families in a sensitive way that enables people to take on board this vital but challenging information is at the heart of what a memory service needs to be able to achieve (Banerjee, 2010).

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It will always be possible to find specific cases where the person with dementia may not want to know, though in reality such individuals are unlikely to have cooperated with the diagnostic process in the first place. But basing practice on such hard cases makes for bad medicine. There is no substitute for a personalized and sensitive approach to the disclosure of the diagnosis, but there is also no avoiding this task.

It is natural that carers should feel protective to family members with dementia. The finding that 83% of carers from an Irish memory clinic did not wish the patient to be told of the diagnosis is often quoted. But the most salient fact from this study is that 71% of the same carers wanted to be told the diagnosis if they developed dementia (Maguire et al., 1996). It is also important to note that this snapshot was taken over two decades ago and public attitudes and understanding are changing. In a more recent study of 50 people with mild dementia, 74% of the carers were willing for patients to be informed of the diagnosis of dementia (Pinner et al., 2003), 98% of carers wanted to know themselves if they had it, and 92% of those with dementia wanted to be told their diagnosis.

A memory service needs to treat communication of the diagnosis as a process, not an event. It is common for patients to use denial and avoidance of a dementia diagnosis as it serves as a coping strategy (Milby et al., 2017), though this is typically followed by a period of reflection and adaptation. Research carried out in this later period suggests that there are often feelings of regret on the part of carers that they had not received the diagnosis earlier so that they could have been more patient, understanding, and less blameful of the person with dementia (Connell et al., 2004). Disclosure of the diagnosis is a necessary prerequisite for future care planning including (with sensitivity) end-of-life care decisions (Derksen et al., 2006; Lawrence et al., 2011). It is self-evident that response to the disclosure of a diagnosis of dementia will depend on the way that this is done. It is an absolute requirement that memory services should do this well from the perspectives of patients and carers. The consultation for the UK NDS found distressingly frequent instances when doctors, thinking that they were doing this well, were in fact doing this badly and potentially doing harm. The following are indicative quotes taken from the NDS (Department of Health, 2008):

I've just been told 'You've got Alzheimer's,' and they walk out; [it] is absolutely bloody disgusting—(person with dementia).

I got the diagnosis on the phone by somebody I had never met telling me, 'Your husband has Alzheimer's and vascular dementia'. That was probably the worst possible way. That was absolutely infuriating—(carer).

I think they need [to be] diagnosing much earlier and take notice of it because I think there are lots of channels that could be avoided if

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the first time they saw you, they got down to business and meant it. Not just fob you off—(person with dementia).

They didn't give me enough information. I came away thinking, 'What do we do now, where do we go from here?' I have a prescription in one hand and a note for blood tests in the other and nobody has said what the CAT scan showed ... nobody has given me that information. I am the person who is going to deal with [my husband]—(carer).

All memory services need standard operating procedures for communicating the diagnosis well that are owned by the whole team and that are delivered consistently. Recommendations for good practice include the following elements (Lecouturier et al., 2008):

1. Preparation
2. Involving family members
3. Exploring the patient's perspective
4. Disclosing the diagnosis
5. Responding to patient reactions
6. Focusing on quality of life
7. Future planning
8. Effective communication

The patient benefits case for memory services

Until recently, little research had robustly evaluated the benefits of accessing memory services, particularly compared to other models. This is in part due to variability in the structures and processes that occurs in different memory services, making it methodologically difficult to disentangle potential effects. Longitudinally, quality of life has been found to improve six months following accessing memory services (Banerjee et al., 2007; Park et al., 2017). Further investigation has identified that, apart from the involvement of Allied Health Professionals, the structure or function of the service had no impact on patient or carer quality of life (Park et al., 2018). Irrespective of patient outcomes, patients and carers that have accessed memory services seem to have positive experiences (Hodge et al., 2013; Hailey et al., 2015), though they often have unmet information and communication needs (Abley et al., 2013).

Some who attend memory services do so only because they are prompted to do so by others, but many will have concerns about their cognitive health. They may have subjective memory complaints or be concerned by an existing family history of dementia. By accessing memory services, these people and their relatives will have the expectation that their concerns will be addressed. However, patient concerns do not always translate into symptoms that meet diagnostic criteria, leading to disappointment. Many of those that do not receive a diagnosis will be reassured that they do not have a dementia and are happy to be discharged from the clinic. But some find no diagnosis or a 'diagnosis' of

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mild cognitive impairment (MCI) and the lack of offered advice and support dissatisfying (Willis et al., 2009). This can lead to people feeling shocked, helpless, and confused about the future (Samsi et al., 2014). Being given the label of MCI can lead relatives to feel disappointed about being discharged from memory services: 'What is quite difficult to take was that it was like "Yeah, there's a problem, it's not that bad. Off you go." ' (Dean et al., 2014). It is therefore essential that memory assessment services are aware of the potential impact of receiving (or not) a diagnosis of dementia, and remain sensitive in the needs of the patients. It also makes clear the need for services to have clear guidance and procedures for the sensitive communication of the absence of a diagnosis or of MCI should be as much of a part of the skill set of memory services as communicating the diagnosis of dementia. Equal consistency in the management of MCI in terms of programming routine reassessment at six to 12 months by the memory service or requiring a further referral would be very valuable.

What happens after diagnosis is of major importance. Post-diagnostic treatment and support is a key component of good quality dementia care. Another area where evidence is lacking but where there appear to be major differences in practice and opinion is the role of memory services in post-diagnosis follow-up. There is major variation in the role that memory services take in providing post-diagnostic care themselves. Many commissioned models require memory services to concentrate only on diagnosis and so to discharge people back to primary care immediately after diagnosis, or soon after, for those with uncomplicated dementia. There seems to be little consistency on the duration, content, and the providers of post-diagnostic support by memory services. In Scotland, the 'Five Pillars Model' of post-diagnostic care is promoted, which states that post-diagnostic support should include (<http://archive.today/XjFoQ>):

1. Understanding the illness and managing symptoms
2. Planning for future decision-making
3. Supporting community connections
4. Peer support
5. Planning for future care

The Scottish Government has guaranteed a minimum of one-year post-diagnostic support (The Scottish Government, 2013), with most individuals needing around eight follow-up meetings in addition to telephone support (Age UK, 2017). Comparatively, current post-diagnostic guidance in England states that follow-ups should be 'systematic' (Barrett and Burns, 2014), which is more open to interpretation. There are very few studies available which evaluate the effect of good quality follow-up and post-diagnostic care for people with dementia and their family carers and the proper role of memory services. However, it is clear that memory services are ideally placed after diagnosis to ensure that people with dementia and their carers start off on their journey of living with dementia equipped with the information and signposting that they need. A good quality system of diagnostic care would be akin to a relay race

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with people with dementia passed safely and securely from one service to another seamlessly. Too often our current disjointed services seem designed to ensure that the baton is dropped, or even lost, for most they serve (Prince et al., 2016).

The economic case for memory services

We finish by addressing the issue of cost. Services must bring value to the people they serve. This value should be measured in terms of the improvements in outcomes that accrue from this service compared to another divided by the cost of the service. If we look at memory services, then it seems very likely that they meet this vital test.

A core aim of the NDS was to ensure that effective services for early diagnosis and intervention are available for all on a nationwide basis. The Strategy accepted that this would require local investment and stated its assessment, and that of HM Treasury, that such a 'spend to save' approach, as advocated by the NAO in its value for money report (2007), could both increase the quality of care and save hundreds of millions of pounds of expenditure over a ten-year period. This is an external validation and endorsement of the clinical and cost-effectiveness of such services.

Gomes and colleagues estimated the costs of memory assessment services six months following diagnosis was on average £1899 per patient (Gomes et al., 2017). However, the incremental net benefit based on the EQ-5D-3L was -£1724 per patient which suggests cost/benefit balance. Such a financial estimate was based on relatively short duration, and therefore did not consider the potential cost savings associated with reduced use of residential care. Banerjee and Wittenberg (2009) modelled the impact of national provision of memory services in preventing admissions to care homes. They estimated the overall savings to society, including savings accruing to public funds and private individuals. The savings increased as the numbers of people prevented from entering care homes increases over a ten-year period. Total annual savings to society from a 6%, 10%, and 20% reduction in the numbers of people with dementia entering care homes would amount to around £150, £245, and £490 million, respectively, by year ten from the nationwide introduction of the early diagnosis and intervention service.

In terms of cost-effectiveness, in the tenth year of the service's operation, its estimated cost would be around £265 million (in 2007/8 prices), taking account of real rises in care costs. If quality of life is factored in, the estimated Net Present Value (NPV) over ten years would be positive, with a gain of around 6250 quality-adjusted life years (QALYs) in the tenth year, where a QALY is valued at £40,000 or 12,500 QALYS if a QALY is valued at £20,000. A gain of 12,500 QALYS would amount to only around 0.02 QALYs per person year. These relatively small improvements seem very likely to be achievable with ease in view of the rise of 4% achieved in the pilot of the Croydon Memory Service (Banerjee et al., 2007). This

intervention would therefore meet stringent accepted definitions of cost-effectiveness (NICE, 2004; Rawlins and Culyer, 2004). Two other cost-benefit analyses provide confirmatory evidence of the potential economic benefits associated with earlier diagnosis and intervention. Both analyses are based on screening programmes in primary care, with savings estimated of a similar order of magnitude at US \$4,000 and \$7,700 per person, respectively (Weimer et al., 2009; Getsios et al., 2012).

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Liaison old age psychiatry

Chapter: Liaison old age psychiatry

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Introduction

The word 'liaison' is defined as communication or cooperation that facilitates a close working relationship between people or organizations (Oxford English Dictionary, 2018). Liaison psychiatry is a sub-specialty of psychiatry that specializes in the interface between physical and mental health, and would typically involve treating patients who are attending general hospitals rather than those who are being cared for in the community or in mental health units. As such, liaison psychiatry involves working closely with staff in general hospital settings. The presence of liaison psychiatry results in a greater recognition of integrated care, and it is now considered a critical service that should exist in all acute hospitals (Royal College of Psychiatrists, 2013a). Although the term *liaison psychiatry* is the most commonly used term, many services operate under the title of Psychological Medicine and it is felt by some that this

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latter term is more representative of the work practised in the general hospitals (Lloyd and Mayou, 2003).

Early liaison psychiatry services focused on those of working age (those between the ages of 18 and 65); however, over time the number of old age liaison psychiatry services has grown due to increased recognition of the need for services aimed at those over 65 years of age, who make up the majority of in-patients in the general hospital settings. At the opposite end of the age spectrum, paediatric liaison psychiatry is also a growing area of interest.

This chapter outlines the development of old age liaison psychiatry, focusing particularly on the UK, including the relevant policies that have influenced this development, and considers current liaison psychiatry service models. It discusses common clinical conditions seen by old age liaison psychiatry services, in addition to other important roles that liaison psychiatrists have in working with general hospital staff, and it also looks at the future of old age liaison psychiatry.

Development of liaison psychiatry

Some consider that psychiatry's establishment as a specialty caring for the 'mentally ill' in the late 1800s resulted in psychiatry becoming increasingly separated from the rest of medicine. Initially, those patients in the general hospital who were referred to psychiatrists were psychotic, had self-harmed, or had disturbed behaviour, with the expectation from the medical teams that those individuals would be transferred to a psychiatric ward (Sharpe, 2014). Over time, a much greater awareness has developed of the benefits of integration and of the value of mental health input for people who primarily need acute hospital in-patient or outpatient care, and a wider range of referrals are now made to liaison psychiatry, including for medically unexplained symptoms.

In the early twentieth century, Barrett recognized the importance of liaison psychiatry, stating: when 'Psychiatry has gained the position of a liaison science between medicine and social problems ... general hospitals and dispensaries should have psychiatric services coordinated among their medical specialties' (Barrett, 1922). Later, in his seminal paper, George Henry (1929) proposed that all general hospitals should have a psychiatrist, and the paper outlined a series of clinical observations, including a number of cases of medically unexplained symptoms that resulted in inappropriate medical and surgical procedures. The term 'liaison psychiatry' itself was reportedly first used in the 1930s to describe the department at Colorado General Hospital in Denver, Colorado (Billings, 1936).

The establishment of liaison psychiatry services continued around the world, but dedicated services were rare in the UK until the 1970s. The founding of the Royal College of Psychiatrists in 1971 was a key step in the development of liaison psychiatry in the UK, as it brought together

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psychiatrists who worked in asylums with those working in teaching hospitals. A special interest group in liaison psychiatry was established in the 1980s, and liaison psychiatry subsequently became a section of the Royal College of Psychiatrists in 1997 and then a Faculty in 2004 (Aitken et al., 2016).

Many liaison teams were originally set up with a focus on the emergency department and have been expanded over time to provide psychiatric input into other areas within the hospital. The rationale for the provision of liaison psychiatry services is to improve psychiatric and medical outcomes of patients, enhance patient experience of medical care, ensure patient safety, and contribute to greater overall cost effectiveness of medical services (Sharpe, 2014). In some areas, there is greater specialization within liaison psychiatry, for example neuropsychiatry, perinatal psychiatry, palliative care, chronic pain, and transplant psychiatry. These are all potentially valuable services that can help to ensure patients have access to the correct care; however, some argue that clinical teams could have more of an impact, and be more sustainable, if they remain flexible and retain their shared service provision (Sharpe, 2014).

Many old age psychiatrists previously worked with patients from a defined geographical area and would care for those patients across the in-patient wards, the community, and in the general hospital. In 2003, it was reported that dedicated liaison psychiatry nurses for older people were only present in 14% of services (Holmes, 2003). However, more hospitals now have a dedicated liaison psychiatry service, which allows key relationships to be developed with the general hospital teams and facilitates better response times.

In 2015, 179 emergency departments in England were surveyed, and 168 reported the existence of liaison psychiatry services. Of these, 150 reported that they worked with older adults, with only five services reporting that they did not see older adult patients; the remaining services did not explicitly report which age groups they worked with. Of the 150 services that saw older adults, only 39 had a separate older adult team within the service, and only 28 of those teams had a consultant old age liaison psychiatrist working within the team (Barrett et al., 2015). In a service evaluation in Newcastle, a 10% yearly increase of older people referred to the dedicated liaison psychiatry service for older people was observed, with the referral numbers to this service being similar to those seen by the local self-harm team (Mukaetova-Ladinska, 2013).

Commissioning and funding of services

In recent years, liaison psychiatry services in the UK have been expanded, especially those in old age liaison psychiatry. Indeed, in 2015 most services reported that they were better resourced than a year earlier (Barrett et al., 2015). As part of the implementation of the Five Year Forward View (NHS England, 2014) NHS England established crisis

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and acute care work streams to support commissioning and provision of 24-hour mental health services, which included £249 million of new funding over a four-year period to expand liaison mental health services. As part of this plan, 50% of all acute hospitals should have a 'core 24' liaison team in place by 2020, meaning that liaison staff would be available 24 hours a day, seven days a week (NHS England, 2016). This document, and the subsequent funding, has resulted in an expansion of many teams across the country; however, the needs of older people are not explicitly stated within the document, and it is important to ensure that any expansion can meet their needs.

In most areas in England, mental health and acute services are provided by separate organizations, 'Trusts', with separate commissioning, and there is also often a physical separation between teams, with many mental health units being situated miles from their catchment general hospital. The funding of liaison services varies across the country, with some being funded via the acute trust, and others from the mental health trust. The services that are commissioned also vary from hospital to hospital—many liaison services continue to focus on the emergency department and self-harm presentations, but others are more integrated into the general hospital wards, with some services being commissioned to provide outpatient services. A number of liaison teams offer follow-up appointments to patients in an outpatient setting, including after self-harm presentations, while other services have subspecialist areas commissioned, such as substance misuse, or specific pathways of care where psychiatry is a core part of the treating multidisciplinary team, e.g. trauma, psycho-oncology, neuropsychiatry, or diabetes. While some hospitals employ psychologists—who are based in separate departments in the general hospital, and are thus separate from liaison psychiatry—many others employ psychologists as a core part of the liaison psychiatry team. A number of liaison teams conduct regular shared clinics with physicians, while Leeds General Infirmary have a National Inpatient Centre for Psychological Medicine, where the care is provided by a range of staff, including liaison psychiatrists and physical healthcare specialists.

The need for liaison psychiatry

The role of the liaison psychiatry team would normally include assessment, diagnosis, treatment, risk assessment, care planning, reviews, and liaison with the medical team, the community mental health team, and primary care. In addition, the liaison psychiatry services would provide relevant training for staff working in the general hospital and would raise awareness of mental health problems and their management.

Thirty per cent of patients with a long-term physical health problem also have a concurrent mental illness (Centre for Mental Health, 2015), which increases the risk of physical health complications and increases the costs of treating the physical illness. The presence of a mental disorder can result in an increased length of hospital stay, and raise morbidity and mortality. It was found that, compared with the general population, the

prevalence of depression is doubled in those with chronic physical illness such as diabetes, hypertension, coronary artery disease, heart failure, and increased threefold in those with stroke, end-stage renal failure, and COPD (Egede, 2007; NICE, 2009). The prevalence of depression is also seven times higher in people with two or more long-term conditions (Moussavi et al., 2007). Patients with COPD have been found to show higher rates of generalized anxiety disorder, panic, and depression, all of which may result in more admissions, longer stays when admitted, and higher relapse rates (Howard 2010).

In addition, it is also well documented that poor mental health can negatively impact on patients' physical health, with a reduction in life expectancy of between seven and ten years with depression, almost 15 years for those using drugs or alcohol, and between ten and 15 years for those suffering from schizophrenia (Chang et al., 2011). Schizophrenia has also been associated with both a threefold higher mortality rate from respiratory disease (Saha et al., 2007), and a twofold increased risk of obesity, diabetes, hypertension, metabolic syndrome, and smoking (De Hert et al., 2009; Foley, 2013), while depression has been demonstrated to have a negative impact on adherence to treatment, including treatment for physical illnesses (Martin, 2005). Liaison psychiatry can help to detect many of these difficulties and can provide support to physical healthcare teams in the management of these patients, with the aim of improving the quality of care received (Department of Health, 2001).

The Healthcare Quality Improvement Partnership (HQIP) has recently placed a significant focus on parity of esteem within their national audits, to ensure that mental health is always considered (Homayoun, 2017). In addition, the National Confidential Enquiry into Patient Outcomes and Deaths (2017) report revealed that there were a large number of patients who had both physical and mental health problems in the general hospital setting. It also suggested that there may be many more patients who had unrecognized mental and physical comorbidity, as not all patients will have had a mental health coding documented on the system. The report also investigated the provision and responsiveness of liaison psychiatry and found that just over 80% of hospitals had a liaison psychiatry service, with the remainder receiving their liaison input via a community mental health team. The report identified significant gaps in care and treatment, which require commitment from the whole organization to ensure that the patient journey is optimized and that seamless referrals to, and timely responses from, liaison psychiatry occur. Twenty-one recommendations were made within their report, including that liaison psychiatry should be fully integrated into general hospitals and be a core part of the multidisciplinary team (The National Confidential Enquiry into Patient Outcome and Death, 2017). As well as setting standards for liaison psychiatry clinical documentation, the report makes recommendations to improve acute hospital staff training and expertise, medication reconciliation, application of Mental Health legislation, and support with alcohol, substance misuse, and smoking cessation. The Care Quality

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Commission (2016) specifically includes mental health in their key lines of enquiry in acute hospitals, including dementia care, use of Mental Health legislation, and access to specialist mental health care.

There has been some debate regarding ageless services, and a number of organizations have begun moving towards this approach. In many areas of liaison psychiatry, there is recognition that there are multiple benefits of having specialists in old age liaison psychiatry and of having access to specialist advice and support for patients with delirium and dementia. Indeed, guidance states that teams should have access to liaison services with recognized experience in treating dementia (NHS England et al., 2016). Eighty per cent of hospital bed days are occupied by someone with comorbid physical and mental illness, mainly the elderly (Parsonage et al., 2012).

In some areas an ageless liaison psychiatry service continues to function, with the same team seeing patients across the age spectrum. However, it is vital that such teams are able to access old age psychiatry experience and expertise if this resource is not available within the team. The National Dementia Strategy supported the commissioning of specialist liaison psychiatry for older people (Department of Health, 2009), and a number of areas have developed old age liaison psychiatry as a separate team from general adult liaison psychiatry, often with some cross cover between the teams.

The National Audit of Dementia in England and Wales is commissioned by HQIP and published by the Royal College of Psychiatrists. The audit programme, which measures acute hospitals against criteria of organizational policies and governance, individual care for the patient and carers, and discharge planning, has recently completed a third round in 2016 and a fourth round is planned in 2018 (Royal College of Psychiatrists, 2017). The second round specifically enquired about access to liaison psychiatry. Nearly all hospitals (94%, 198/210) reported having access to a liaison psychiatry service, and 85% (168/198) of these were able to provide emergency or urgent assessments. Of the hospitals with access to a liaison psychiatry service, 82% (162/198) had a named Consultant Psychiatrist lead, which was an improvement from 75% of hospitals in the first audit conducted in 2010. Sixty-eight per cent (135/198) had a Consultant Psychiatrist with older adult experience who had dedicated time for the liaison service, an improvement from 50% the previous year. Ninety-six per cent (189/198) reported the service to be provided by a specialist mental health team, but only 69% (130/189) of hospitals said that the liaison team would regularly provide routine mental health care to both adults and older adults services. Indeed, 28% (52/129) of hospitals stated that they only covered adult liaison psychiatry, while only a third of those with access to a liaison psychiatry service had access to older adults' expertise 24 hours a day (Royal College of Psychiatrists, 2013b).

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Service models

Several different service models for liaison psychiatry have been developed over time, and the models are still rapidly changing and developing. Models and standards for old age liaison psychiatry have not been explicitly specified, but many services view old age liaison psychiatry as having to adopt the same standards as the corresponding working age liaison psychiatry services. Fig. 24.1 shows the structure of a fully integrated liaison psychiatry service.



Fig. 24.1
Example of fully integrated liaison psychiatry service.

A number of the models that have been developed can be categorized according to the approach that staff take regarding how rapid the response time is and how pro-active the liaison psychiatry team can be in the general hospital. National guidance in England is that patients referred as an emergency should be seen within one hour, urgent referrals should be seen within one working day, and routine referrals should be seen within two days of the referral (Royal College of Psychiatrists, 2013a). Services can also be categorized by the number of hospital beds and level of staffing.

There are five key approaches to liaison psychiatry, some of which overlap:

1. A consultation model, also known as consultation-liaison psychiatry
2. A liaison model, where the approach is much more integrated.
3. The Rapid Interface and Discharge (RAID) model
4. A proactive liaison psychiatry model
5. Mental Health Partnerships' Models for Liaison Psychiatry Services.

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Consultation model

Consultation liaison psychiatry emerged in the United States, and developed throughout the 1970s. In the consultation model, the referring doctor, or other member of the referring team, would have to request a psychiatric assessment or advice. Following assessment, the psychiatry team would make recommendations on a case by case basis; however, the general hospital team would be responsible for the management of that intervention.

Liaison model

Benefits of a more integrated approach than that offered by a consultation liaison psychiatry model have been recognized for a number of years. The differences between the consultation model and a liaison psychiatry approach were described in 'Who Cares Wins' and the comparison has been adapted and updated in Table 24.1 (Royal College of Psychiatrists, 2005). The liaison approach is designed to integrate the assessment and treatment of patients with mental disorders into the routine practice in general hospitals, with liaison psychiatry staff having a greater presence in the hospital and routinely collaborating with colleagues across other specialties. Importantly, the model is not limited to direct patient contact, incorporating other tasks such as education and training, service development, and quality improvement into its remit (Fig. 24.1). The service is intended to be proactive, and a systematic review in 2000 demonstrated that this approach was associated with a number of advantages, including better diagnostic accuracy by those referring patients to the service, and increased adherence to recommendations made by the psychiatry team (Draper, 2000).

Table 24.1 Differences between consultation and liaison psychiatry.

Consultation	Liaison
Reactive	Proactive
Limited resources	Intensive resource use
Isolated working	Collaboration with colleagues
Hospital referrals are a low priority	Hospital referrals are a high priority
Limited impact of liaison service	Impact demonstrated of benefits
Slow response to referrals	Rapid response to referrals

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Fewer referrals made	More referrals made
Limited review of patients	Frequent patient reviews
Poor-quality referrals	Better referral quality
Poor adherence of the treatment plan by the clinical team	Improved adherence to the treatment plan
Practice of hospital staff not altered	Changed practice of hospital staff
Mental health separate from general services	Mental health integrated with general services
No change on length of stay	Reduced length of stay in hospital
	Better patient satisfaction

Adapted with permission from Who cares wins: improving the outcome for older people admitted to the general hospital. Working Group of the Faculty of Old Age Psychiatrist, Royal College of Psychiatrists, London. The production of this document has been funded by the Faculty of the Psychiatry of Old Age, Royal College of Psychiatrists. Copyright © 2005 The Royal College of Psychiatrists.

Many organizations provide a service that would be considered to be somewhere between these two models, where services remain reactive and require referral, and many patients are only seen once. However, compared with when the 'Who Cares Wins' document was published, liaison services have developed considerably over the last decade. There is now more collaboration with colleagues in the general hospital and better teaching opportunities in mental health for the general hospital staff, and hospital referrals are a high priority in the presence of a dedicated service.

RAID model

The Rapid Assessment, Interface and Discharge (RAID) model was established in Birmingham in 2009 as a single point of access, multidisciplinary service, available 24 hours a day. This model was developed to have a greater focus on response times, with a one hour target response time to assess patients referred from A&E for emergencies, and a 24 hour response time for those referred from in-patient wards. An evaluation of the economics of this service was undertaken by the London School of Economics and the Centre for Mental Health in 2011 (Parsonage and Fossey, 2011; Tadros et al., 2013).

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The service was shown to significantly reduce the rate of readmission, from 15 readmissions down to four readmissions for every 100 people. Combined with a reduction in the average length of stay, which was observed mainly in older patients, this decrease in readmission rate resulted in an estimated saving of 8,100 bed-days per year, enabling the hospital to close 60 of their 600 beds without cutting services. The study found that for every £1 invested in liaison psychiatry, there would be a £4 return, with most savings being for those over the age of 65, demonstrating the cost-savings that could result from the presence of a liaison psychiatry service (Tadros et al., 2013). The RAID study was not randomized, but the model has since been developed in a number of organizations.

Proactive liaison psychiatry model

Two studies in the US have shown promise in a proactive model to reduce length of stay. Desan and colleagues (2011) compared proactive care including brief review of all admissions, rapid consultation, and follow-up with usual practice of reactive consultations. The number of reviews and caseloads were predictably higher, but costs more than offset by savings in length of stay.

In 2015, Sledge and colleagues (2015) introduced a proactive behavioural intervention team in Yale-New Haven Hospital, where patients were discussed with the medical team, case reviews taking around three minutes for each patient. They found that over 50% of the patients that they screened within the timeframe had mental health needs, and 23% of patients received a psychiatric consultation, in comparison with only 11% of the control group. The introduction of the intervention team resulted in a reduced time between referral and consultation, and a decreased average length of stay in the general hospital.

In contrast to the findings described here, a randomized, double-controlled clinical trial of proactive consultation was conducted on the general medical in-patient services of a university hospital, with the main outcome measures being length of hospital stay and hospital costs. Hospital resource use decreased in the entire sample over 21 months and it was found that a single experimental psychiatric consultation did not reduce costs (Levenson, 1992).

HOME, a large multi-centre randomized controlled trial is currently being conducted in the UK in those aged 65 and over. In this trial, three Trusts in England will be randomizing patients to proactive liaison psychiatry or usual care, even when no mental illness is evident, to determine if there is an impact on discharge date from input from liaison psychiatry (see The HOME study: <https://oxfordpsychologicalmedicine.org/research/thehomestudy/>).

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Mental Health Partnerships' models for liaison psychiatry services

Four models of liaison psychiatry were described in the Mental Health Partnerships' 'Guidance on Developing Models for Liaison Psychiatry Services', with the intention of setting the minimum service requirements needed to attain the cost and quality outcomes that the evaluation of RAID suggested were possible. The recommendations in the guidance resulted from adapting the RAID model and other services to provide models for hospitals of various sizes, with and without emergency departments and with varying demands across the 24-hour period (Aitken et al., 2014c):

- Core: Liaison Psychiatry Services that operate working or extended hours only, intended for services where there is variable demand across the week, including periods of no demand, and where a 24-hour staffed response would not be economical.
- Core 24: Liaison Psychiatry Services that operate 24 hours a day, seven days a week, intended for services where there is sufficient demand to warrant a full 24-hour service.
- Enhanced 24: Liaison Psychiatry Services that operate 24 hours a day, seven days a week with extensions to fill local gaps in service and some outpatient services, intended for services where enhancements to the minimum specification are required to fit in with gaps in existing pathways and services.
- Comprehensive: Liaison Psychiatry Services that operate 24 hours a day, seven days a week, enhanced with in-patient and outpatient services to specialties, which would tend to be found in large secondary care centres with regional and supra-regional services (Aitken et al., 2014a).

NHS England have stated that 50% of all acute hospitals should have a Core 24 liaison team in place by 2020, meaning that liaison staff would be available 24 hours a day, seven days a week.

Table 24.2 shows example staffing requirements and costs for each of the different service types. The setup of services will vary due to the local demand and circumstances; for example, some teams have larger consultant numbers and lower nursing numbers. There are also many hospitals whose bed numbers fall between the 500 and 2000 beds outlined in the example models (Aitken et al., 2014a).

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Table 24.2 Example requirements for the different service models.

	Core	Core 24	Enhanced 24	Comprehensive
Example number of beds	500	500	500	2000
Consultants	2	2	4	5
Other medical	0.6	2	2	2
Nurses	2 band 7 (team leader), 6 band 6	6 band 7, 7 band 6	3 band 7, 7 band 6	2 band 8 17 band 6 10 band 5
Other therapists	0	4	2	16
Team manager	1 band 7	1	1	3
Admin—band 2, 3, 4	2.6	2	2	12
Clinical services manager	0.2 band 8	0.2–0.4	0.2–0.4	1
Business support band 5	0	1	1	1
Total WTE	14.4	25.2–25.4	22.2–24.4	69
Hours of service	9–5	24/7	24/7	24/7

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Age	16+	16+	16+	16+
Older person	Yes	Yes	Yes	Yes
Drug and alcohol	No	Yes	Yes	Yes
Outpatient	No	No	Yes	Yes
Specialties	No	No	No	Yes
Cost	£0.7M	£1.1M	£1.4M	£4.5M

Reproduced with permission from Aitken P, Robens S., Emmens T. (2014c). Developing Models for Liaison Psychiatry Services – guidance, Strategic Clinical Network for Mental Health, Dementia and Neurological Conditions South West Strategic Clinical Network, <http://mentalhealthpartnerships.com/wp-content/uploads/sites/3/3-developing-models-for-liaison-psychiatry-services.pdf>.

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Clinical aspects of old age liaison psychiatry

In a general hospital setting, over two-thirds of beds are occupied by patients aged over 65 (Department of Health, 2009). In liaison psychiatry, referrals may come from any team in the hospital, which requires a flexible approach. There are a number of particular challenges associated with assessments in general hospital wards, including a lack of privacy to perform the assessment. Interruptions are also common, and it is not unusual for the patient to be unaware of the referral to the liaison psychiatry team. It is therefore important to check that the patient understands why the referral to liaison psychiatry was made prior to the assessment. Ideally, referrals will articulate the specific question to which the referring team would like an answer; however, it is often the case that such questions are not included in the referral, and it is also important to bear in mind that other useful information may come from the assessment that could influence the management plan.

There are a number of reasons why patients are referred to liaison psychiatry services from the acute hospital. Some patients have a pre-existing diagnosis of a mental disorder and require specialist input during an admission with a physical health problem. Others may develop or reveal a psychological illness during their time in hospital, for example, delirium, depression, anxiety, or psychosis. In some cases, these conditions may be related to their physical health or treatment. Emergency referrals to liaison psychiatry are often related to self-harm, suicide risk, or acute behavioural disturbance. Moreover, liaison psychiatry clinicians may be asked to assist with complex capacity decisions, or with discharge planning. It has been reported that 70–80% of referrals are from medical departments, and around 5% of patients referred require in-patient psychiatric treatment, with 10–20% being referred to community teams (Anderson and Ooman, 2012).

Some of the more common conditions seen by old age liaison teams are:

- Depression
- Dementia and cognitive impairment
- Delirium
- Alcohol problems
- Behavioural disturbance.

In addition, liaison psychiatrists are also called on to provide advice on relevant legal frameworks, especially in cases where capacity is lacking and the patient presents a risk of harm to themselves, or requires detention under the Mental Health Act.

Little information is currently available in the literature analysing referrals to old age liaison services, but it is likely that more data will become accessible over the coming years. In the local service at Addenbrookes Hospital, Cambridge, the total number of referrals to older

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people's liaison psychiatry over a one-year period commencing 1 April 2016 was 1,487, which led to 1,300 face-to-face assessments, in addition to 187 cases where only advice was required.

There were a number of reasons for patients being referred to this old age liaison service. In many cases, the patient was not referred for a single reason, the referral arising from a combination of issues. The most common reason was for a mental health assessment (1,262 cases), followed by requests for a medication review (887 cases). Patients were also referred to the team for advice on placement or discharge plans (369 cases), Mental Capacity Act assessments (256), contribution to the multidisciplinary management and education (217), and carer's education and support (172). Table 24.3 summarizes the mental health diagnostic outcomes of patients assessed over this 1-year period in Addenbrookes Hospital (Wai, 2017).

Table 24.3 Number of patients seen by old age liaison psychiatry in Addenbrookes Hospital with particular psychiatric diagnosis over a one-year period.

Diagnosis	Number of patients
Delirium	428
Dementia	415
Depression	271
No active mental health problem	121
Anxiety	79
Alcohol-related disorder	33
Schizophrenia	31
Bipolar affective disorder	29
Adjustment disorder	13

These data contrast with those reported by Guthrie (2016) for referrals to a working age adult service, where the most common diagnosis was depression, followed by schizophrenia and bipolar affective disorder.

Some of the common conditions seen by old age liaison psychiatry teams are outlined in the next few subsections. More detailed information about each of the conditions can be found in other relevant chapters; the

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objective here is to consider the assessment and management of these conditions in a liaison setting.

Depression

A systematic review of depression in general hospital settings revealed the median prevalence to be 10%, but there was a wide variation of 3–52%, which related to different diagnostic criteria being used and the different medical specialties being considered (Walker et al., 2016). There is thought to be a higher risk of the development of depression with neurological disorders, HIV, cancer, and chronic pain than for other diagnoses. Rayner and colleagues (2010) concluded that antidepressants were effective compared with placebo in seventeen studies that included patients with a range of physical illnesses, including cancer, diabetes, heart disease, lung disease, renal disease, HIV, head injury, multiple sclerosis, stroke, and mixed somatic diseases.

Shoar and colleagues' (2016) study in surgical patients showed that depression at the time of admission was significantly associated with longer hospital stay, a previous history of mood disorders, the need for surgery or reoperation, underlying diseases, surgical complication, and lack of familial support.

The assessment of depression in general hospital settings may be complex as it has to be differentiated from an acute stress reaction related to a serious concurrent health condition. Communication difficulties associated with disorders such as acute stroke, in addition to sensory impairment, may also present challenges for assessment.

Treatment options include pharmacotherapy and psychological treatments, and there may also be a number of social issues, which liaison psychiatry can help to resolve. Liaison psychiatrists may also be able to help to identify precipitants arising from the ward environment, for example, profound social isolation resulting from prolonged care in a side room. It is important to consider any risks of self-harm or suicide and to put in place a plan to mitigate any ongoing risks, for example, one-to-one nursing observations. Other risks of depression include the adverse outcomes of the patient's physical health conditions, for example, suboptimal rehabilitation following hip fracture due to reduced motivation and/or falls anxiety, reduced treatment adherence, or unwillingness to engage with discharge care planning. Due to tight timelines for rehabilitation decisions, there is often limited time available in liaison psychiatric practice to decide whether or not to instigate antidepressant treatment, and rapid decisions may be needed for patients with severe depression who are refusing food and fluids.

Dementia and cognitive impairment

Sampson and colleagues (2009) reported the prevalence of dementia in the general hospital to be 23.2% in those aged 70–79 and 65.5% in those over 90 years of age, but only half of these patients had been diagnosed

with dementia prior to admission, indicating significant unmet need in the community. The vast majority of acute hospital admissions for people with dementia occur in an emergency, and many emergency presentations in people with dementia are preventable (Aitken et al., 2014b). As the population ages, increasing numbers of people will die with dementia, many in an acute hospital. The rising prevalence of dementia is important, as additional resources will be required for intermediate and palliative care, and for the provision of mental health liaison services for patients with dementia. The most common cause of dementia is Alzheimer's disease followed by vascular dementia, mixed Alzheimer's and vascular dementia, and then Lewy body dementia.

Cognitive impairment is commonly found in older people over the age of 65 who are admitted to hospital as an emergency (Reynish et al., 2017). One study described 'cognitive spectrum disorder' (CSD) as a composite of delirium, dementia, or Abbreviated Mental Test (AMT) score < 8/10, in patients in the general hospital; CSD was present in almost 40% of those over the age of 65 and in over half of those over the age of 85, and resulted in an increased length of stay in hospital (Reynish et al., 2017). A superimposed delirium was reported in 46% of patients with dementia, and higher mortality rates have been reported in patients with severe cognitive impairment (Reynish et al., 2017; Sampson et al., 2009).

The most recent National Audit of Dementia showed that the majority of hospitals have dementia champions, but staff reported that they needed more support, especially out of hours. Recommendations from the audit included an initial screening or checks for delirium, better accessibility to key personal information related to care needs, closer attention to meeting nutritional needs, and higher-level support from dementia champions, ensuring the availability of a dementia champion to support staff at all times. It was also felt that the person with dementia needed to be more involved in decision-making, and so further training for staff on consent, best interest decision-making, lasting power of attorney, and advance decision-making was required (Royal College of Psychiatrists, 2017).

Delirium

Delirium is common in the general hospital setting, affecting around a fifth of adult in-patients, especially if the patient has an existing cognitive impairment (Ryan et al., 2013). However, it can affect as many as 60% of older adults (NHS Confederation, 2009). Despite its relatively high prevalence, delirium remains undetected in significant numbers of patients. Indeed, one study found that delirium was undetected in 72% of cases (Collins et al., 2010). Delirium is sometimes classified into hyperactive, hypoactive, and mixed. Multiple causes of delirium are well known, including infection, biochemical disturbance, acute organ failure, and medication. Prevention and recognition of this condition are important. Features of delirium may include: fluctuations of mental state; impaired cognitive function, especially attention and orientation; clouded

consciousness; psychosis especially visual hallucinations; altered sleep-wake cycle; and motor disturbance (Stern, 2010).

In some cases, the cause of the delirium is not clear. It is important for the liaison teams to ensure that a physical cause has not been missed and to work with the treating team to ensure that relevant investigations have been performed. The adjusted hazard ratio of a patient dying during an admission if they develop a delirium has been estimated to be 3.5, with raised mortality persisting for up to five years after an episode of delirium (Eeles et al., 2010). Other negative outcomes of delirium include increased length of stay and discharge to institutional care.

The acute hospital should have systems in place to identify those at risk of delirium and to prevent its development. Common predisposing factors for the development of delirium include older age, dementia, severity of medical illness, infection, multiple high-risk medication, catheterization, immobility, sensory impairment, urea and electrolyte disturbance, and malnutrition (Ahmed et al., 2014). The potential to prevent delirium is well established. Inouye and colleagues (1999) showed that the introduction of protocols for the management of six risk factors (cognitive function, sleep, mobility, visual impairment, hearing impairment, and hydration) reduced the incidence and duration of delirium.

Treatment of delirium should focus on the underlying cause, and nonpharmacological interventions to manage the patient's behaviour are essential. A safe environment without access to dangerous objects is crucial, and one-to-one nursing care, avoiding excessive sensory stimuli, providing natural daylight in the day, ensuring a working light source above the patient's bed to help reduce misperception, and a visible clock and calendar to facilitate orientation are also useful. Reducing ward moves and ensuring access to glasses and hearing aids can also help with the symptoms of delirium. If possible, it can be helpful to limit the changes in staff members caring for the patient and staff should be encouraged to introduce themselves to the patient and explain what they are doing each time they are interacting with the patient.

At times, pharmacological therapy is essential in the management of the behaviour. Unless contraindicated, a small dose of haloperidol or an atypical antipsychotic can be used first line. Antipsychotics should not be given to patients with a diagnosis of Lewy body dementia and, in those cases, benzodiazepines may be required.

Alcohol

Detection of alcohol problems in the general hospital setting is important, as early recognition can help to prevent delirium and reduce unnecessary investigations. Physical signs to look for include tremor of tongue and hands, excessive capillarization of facial skin and conjunctivae, bruising and other injuries, alcohol on breath, obesity, hypertension, and an enlarged liver. The CAGE screening questionnaire can be helpful to check

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for features of dependence: this screening tool asks if people think that they should Cut down on their drinking, if people have Annoyed them by asking them to cut down on drinking, if they ever feel Guilty about their drinking, and if they have had an Eye-opener, i.e. a drink in the morning to steady their nerves (Ewing, 1984).

To identify those at greater risk of alcohol withdrawal, alerting features are alcohol on the patient's breath, the patient drinking over half a bottle of spirits or equivalent a day, morning tremor or relief drinking, previous withdrawal symptoms, elevated MCV and/or GGT, and co-dependence on other substances, e.g. benzodiazepines. In the first 24 hours, there is often apprehension, tremor, insomnia, nausea, vomiting, and tachycardia; however, clinical teams should also be alert to unexplained delirium or agitation during recovery periods following emergency admissions for people with unrecognized alcohol use disorder. The Clinical Institute Withdrawal Assessment for Alcohol—Revised (CIWA-Ar) is a ten-item tool that can be useful to monitor withdrawal. It is not a diagnostic tool, but it can be helpful in assessing withdrawal severity and for titrating pharmacotherapy (Kattimani and Bharadwaj, 2013). Chlordiazepoxide can be used to relieve withdrawal symptoms and is commonly prescribed as a reducing regime. Oral thiamine is poorly absorbed, and so systemic replacement of the thiamine is essential to help prevent Korsakoff's syndrome and Wernicke's encephalopathy. Pabrinex is therefore an essential treatment, and would normally be given intravenously in the general hospital setting. Signs of Wernicke's include disordered mental state, oculomotor abnormalities, gait ataxia, and polyneuropathy (Liow, 2017). The elderly population have an increased risk of delirium compared with younger patients, and it is also important to consider the misuse of illicit drugs, prescription drugs, or over the counter medication in the elderly.

Behavioural disturbance

Patients are frequently referred to liaison services because of concerns about their behaviour. It is important to gather information about a pattern of the behaviour and potential triggers, in addition to identifying the reason for the change in behaviour, for example, if the patient is in pain, intoxicated, depressed, psychotic, withdrawing from alcohol, experiencing a delirium, or are they exhibiting behavioural and psychological symptoms of dementia. For patients with dementia, it is helpful to obtain a clear history from ward staff about challenging behaviour, for example, wandering could be caused by agitation or forgetfulness, while aggressive behaviour may be spontaneous and random, occurring at particular times of day e.g. sundowning, or associated with nursing interventions. Information from the patient, family, or carers, in addition to ward staff, is essential in putting a care plan together to manage the behaviour. Nursing staff in the general hospital may need additional support to help them to manage the patient's behaviour and it is helpful if they can record a behaviour chart

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to look at potential triggers and interventions that help with the behaviour.

Capacity/legal frameworks

Thousands of decisions about patient care are made every day in acute hospitals, and patients' ability to participate in decisions should be assumed. Mental capacity legislation is designed to protect people and to empower those who may lack capacity to be as involved in decision-making as possible, especially for serious or irreversible decisions.

The Mental Capacity Act 2005 in England and Wales is designed to empower those working in health and social care to assess capacity without reliance on mental health professionals. A two-stage capacity test can be used by anybody who cares for or treats a person who may lack capacity. The first stage of this test is to determine whether or not there is an impairment of, or disturbance in, the functioning of a person's mind or brain; the second stage is to determine if the impairment or disturbance is sufficient to impact on the capacity to make a decision by assessing whether the patient can understand the information, retain the information long enough to make a decision, weigh up the pros and cons, and communicate their decision (Department for Constitutional Affairs, 2013).

However, it is possible that an expert opinion will be required for particularly complex cases or for major decisions (SCIE, 2016). In such cases, a referral to liaison psychiatry may be made, and they should work alongside the treating team, the patient and their family or carers to assess capacity (Fig. 24.2). If the patient lacks capacity, a best interest decision should be made, which may also involve a psychiatric opinion to consider the impact of the various options on the person's psychological wellbeing.

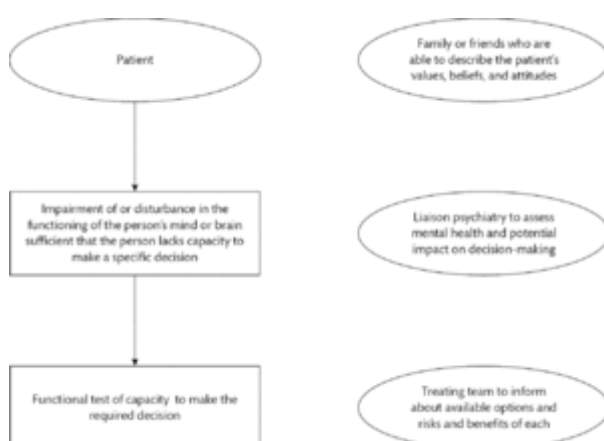


Fig. 24.2

The contribution of liaison psychiatry in complex capacity assessments.

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In addition, there may be patients on an older adult ward who do not wish to stay on the ward, but lack capacity to consent to the admission or to understand the reason for the admission. Consideration about whether there is a deprivation of liberty, which would result in a breach of Article 5 of the European Convention of Human Rights, is essential as well as deciding which legal framework to use. In England, the Mental Capacity Act 2005 and the Mental Health Act 1983 (amended 2007) are the statutes that are frequently referred to. The Deprivation of Liberty Safeguards is part of the Mental Capacity Act and would often be used in the general hospital when the patient was primarily there due to their physical illness in cases where they were being deprived of their liberty and lacked capacity to agree to the admission. In some cases, for example, where a patient has a severe depression but continues to require medical treatment, consideration for the Mental Health Act, or equivalent legislation, may also be required. Alternative legal frameworks exist in other jurisdictions.

Case examples

The following boxes highlight few case examples where old age liaison psychiatry may be involved.

Case study 1

Mary is a 68-year-old lady who was admitted to a respiratory ward with an acute exacerbation of COPD. She was receiving antibiotic treatment and the respiratory team optimized her COPD treatment. However, subjectively, she felt that her breathing was deteriorating despite the treatment that she was receiving. Mary was assessed by the liaison psychiatry team, and it was felt that she had an anxiety disorder that was impacting on her breathing. Based on the assessment, the liaison psychiatry team worked with her to identify thoughts and behaviours related to her breathlessness and delivered brief psychological therapy. Her breathing and the control of her COPD improved.

Case Study 2

Jack is a 70-year-old man who was in hospital after an attempt to end his life that occurred following the death of his wife. He had taken a large overdose of medication that belonged to him and his wife. He required treatment on the medical high dependency unit and was referred to liaison psychiatry who saw him when he was still requiring medical treatment. He had experienced symptoms of severe depression for several months, but had not wanted to seek help from his family or GP as he felt embarrassed. He had no

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previous history of mental illness and did not want to admit how low and hopeless he had been feeling. During his time in hospital, the liaison psychiatry team were able to see him daily, which allowed them to develop a therapeutic relationship, encourage a helpful openness with his family network, consider psychosocial interventions for depression, and commence anti-depressant treatment. On discharge from hospital, Jack was referred to the crisis team who were able to work closely with his family to manage risk and monitor his response to antidepressants.

Case Study 3

Peter is a 66-year-old man who was on a rehabilitation ward following a cerebrovascular accident. He had previously been fit and well, was working and was an active member of the local community. During the first two weeks following his stroke, he had been low in mood, irritable and had not engaged in rehabilitation. He was referred to liaison psychiatry. A psychosocial formulation was used to highlight the personal difficulty he had in adjusting to uncertainty and a lack of control over his daily routine. The multidisciplinary team on the ward used this understanding to adapt his care to meet the needs of his personality and values. He regained a sense of control and hope, and subsequently his progress through rehabilitation improved.

An example of an integrated service in diabetes care

One example where liaison psychiatry has been shown to have a significant influence is in diabetes. It was reported that the prevalence of diabetes was 6.6% of the UK population aged 20-79 in 2013, and this prevalence was projected to increase to 7.4% by 2035, while worldwide age-standardized prevalences in 2014 were 9.0% for men and 7.9% for women (Guariguata, 2013). Twenty per cent of people aged over 75 are reported to have diabetes (Meneilly et al., 2001), and the vast majority of cases are reported to be due to Type 2 diabetes (NCD Risk Factor Collaboration, 2016). Poor diabetic control can lead to significant complications, including blindness, renal failure, or amputation (Hippisley-Cox and Coupland, 2016).

Depression is the most common psychiatric comorbidity with a prevalence of 10–30% (Doherty, 2016). Patients with diabetes may struggle to adapt to their condition, and there may be a fear, especially in type 1 diabetes, of hypoglycaemia. In addition, some diabetic patients experience needle phobia, and diabetes can complicate the management of an eating disorder as omitting insulin can promote glycosuria.

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Interventions can include pharmacotherapy with antidepressants, and psychotherapy, including motivational interviewing.

King's College, London established a 3DFD scheme in 2010, which stands for three dimensions of care for diabetes. This scheme assesses 300 patients a year who have diabetes and a comorbid mental illness, including needle phobia, depression, or anxiety. Over half of these patients had a new diagnosis of a psychiatric disorder, which illustrates that there was a considerable unmet need prior to the establishment of the service. Introduction of the service resulted in a significant drop in attendances to the emergency department, fewer admissions to the general hospital, and was estimated to save £850 per patient over a one-year period—a saving that is anticipated to increase over time (Doherty et al., 2016).

A collaborative project between liaison psychiatry and the diabetes services in Cambridge incorporated a Psychological Wellbeing Practitioner into the diabetic service in order to promote psychological wellbeing. They were able to screen for common mental health problems, signpost, and provide a brief intervention. In cases where there were more complex problems, a stepped care pathway approach was used and a psychologist or psychiatrist from the liaison team was able to become involved. There were significant improvements reported in both physical and psychological outcomes and staff satisfaction also improved.

Use of rating scales or screening tools

There are a number of different screening tools available for use by staff in the general hospital to help them to identify patients who have symptoms that are suggestive of a psychological problem or a psychiatric illness, and who require referral to liaison psychiatry. These tools include ultra-short screening instruments, and their use varies between hospitals and between departments in each hospital.

Some of the tools, for example, those used for anxiety and depression, can be affected by the presence of some physical illnesses, as sleep and appetite disturbance accompany both physical and mental illnesses, particularly in a general hospital environment; caution is therefore needed when interpreting tools that incorporate these measures. The Hospital Anxiety and Depression scale is a self-rated scale developed with the aim of detecting anxiety and depression in patients who have physical health problems. Importantly, it does not include sleep or appetite disturbance, but instead focuses on cognitive symptoms of both disorders. It comprises a 21-point scale, and scores of 11 or more on either the anxiety or depression sub-scales are proposed as indicating the presence of an anxiety or depressive disorder (Zigmond and Snaith, 1983). The Geriatric Depression Scale is another tool that is available to clinicians. It is a 30-item questionnaire, which can take some time to complete, although a 15-item and four-item version are available (Yesavage, 1982).

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Cognitive testing is often carried out in general hospital settings using the Mini-Mental State Examination (Folstein et al., 1975) or the Abbreviated Mental Test. More detailed assessment can be undertaken using the Addenbrookes Cognitive Examination or longer batteries of tests. However, physical illness, impaired vision or hearing, educational background, depression, or anxiety can affect the score, so it needs to be interpreted along with a history from the patient and collateral history in order to facilitate a diagnosis.

Screening for delirium is commonly done by The Confusion Assessment Method (CAM) which is based on DSM-III-R and takes around five minutes to administer. However, use of this tool requires training. An alternative is the Delirium Rating Scale, a ten-item scale based on the patient's behaviour over a 24-hour period, and the Delirium Rating Scale—Revised 98, a 16-item scale; however, these latter two tools should only be used by those with training. The 4AT test consists of four items, two brief cognitive tests, assessment of level of consciousness, and an acute change in mental state (4AT, 2011). Advantages of this test are that it can be used without specific training and it is easy to use with a good sensitivity and specificity (Bellilli et al., 2014).

Outcomes

As a result of the increased focus within healthcare on outcome measurements, the Framework for Routine Outcome Measurement in Liaison Psychiatry (FROM-LP) was developed. This framework aimed to solve the challenges in developing outcome measures in liaison psychiatry where services vary in content and quality, and also where a service operates in many clinical environments with different patient groups (Royal College of Psychiatrists, 2015). It includes clinician-rated clinical outcomes, patient-rated clinical outcomes, patient-rated satisfaction, and referrer-rated satisfaction (Royal College of Psychiatrists, 2015). The recommendation was that FROM-LP should be adopted across all liaison services to facilitate data collection and effective reporting of outcomes. Outcome measurement tools should assess performance, service quality, and cost-effectiveness. FROM-LP uses the Identify and Rate the Aim of the Contact model and it gathers information about response times of the liaison service; however, it does not consider time of referral to liaison psychiatry from the point of admission (Tadros, 2016).

Training in liaison psychiatry

Liaison psychiatry has developed significantly in recent years, particularly for older people. Higher trainees in general adult psychiatry in the United Kingdom have been able to receive an endorsement in their training in liaison psychiatry through the Royal College of Psychiatrists since the late 1990s, if they undertook a year of training in an accredited liaison psychiatry post. Since 2016, trainees in older adult psychiatry have also been able to gain a similar accreditation in liaison psychiatry, which is a demonstration of the increased importance of this area (Burn,

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2016). There are also a number of paediatric liaison posts being developed in several areas, but there is currently no formal accreditation in child and adolescent mental health training.

Nursing staff working in liaison psychiatry teams are experienced mental health practitioners. It was previously recognized that there was a need for competencies for liaison nurses to be developed, and this task was undertaken by the London Wide Liaison Nurses Special Interest Group. The latest revision included competencies specific to different patient groups, including older adults (Eales et al., 2014).

Teaching and education

One of the key roles of a liaison psychiatry service is to provide training for the general hospital staff. This teaching or training can be undertaken in a variety of formats, depending on local demand and requirements. Formal teaching programmes can be established with key staff groups, for example, on dementia, delirium, self-harm, managing disturbed behaviour, legal frameworks, and recognizing psychiatric disorders. Informal teaching is also important on the wards when discussing referrals and when feeding back information about patients that have been seen. Attendance at the medical grand round is also useful, and several organizations run Schwartz rounds, where the focus is on the social and emotional issues in particular cases; these sessions can help facilitate joint learning across all staff working in the general hospital (see <http://www.theschwartzcenter.org/supporting-caregivers/schwartz-center-rounds/>).

Accreditation of services

The Royal College of Psychiatrists College Centre for Quality Improvement (CCQI) run a number of accreditation schemes across different services. The Psychiatric Liaison Accreditation Network (PLAN) accreditation is designed to assure and improve the quality of liaison psychiatry services. It also facilitates the networking of different teams through e-mail discussions and events. Services that meet the required standard are awarded accreditation for a three-year period, with an interim review (see <http://www.rcpsych.ac.uk/workinpsychiatry/qualityimprovement/qualitynetworks/liaisonpsychiatry/plan.aspx>). Examples of improvements that have been made by teams as a result of PLAN accreditation include the provision of better assessment rooms, better training for the liaison team, improved policies and procedures, and better information being provided to patients (Palmer et al., 2016).

Interfaces

Where liaison psychiatry services are embedded within the mental health Trust, it is important to consider the joint governance arrangements with the general hospital Trust as the liaison psychiatry team will work across both organizations. Liaison psychiatry teams often contribute to relevant

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policies and guidance within the general hospital, and joint meetings between the relevant managers should be established.

In addition to good working relationships and collaboration with colleagues in the general hospital, another important role of liaison psychiatry is to ensure good interfaces with other mental health colleagues who work in the psychiatric in-patient units and in community care. Many of the patients will require ongoing support or review within psychiatric services once they leave the general hospital, and it is essential for the liaison psychiatrist to be able to facilitate that ongoing support. Collaboration with primary care is also essential, as GPs and general practice staff provide significant input into the care of patients once they leave the general hospital.

The future of liaison psychiatry and integrated care

Liaison psychiatry has shown significant expansion over recent years. However, there is further research underway investigating the benefits of more proactive models of liaison psychiatry, and the recognition of the importance of integrated care is increasing. Additional research is still needed into the benefits of liaison psychiatry and the potential input of liaison psychiatry into different specialist areas, e.g. as with diabetes.

Further development of a liaison model in primary care may be seen in the future and additional work may be done to promote admission avoidance in the general hospital. There are plans within the five year forward view to improve psychological therapy access and to integrate physical and mental health (NHS England, 2014). An example of improved integrated care is the involvement of Improving Access to Psychological Therapies (IAPT), which have now expanded into physical healthcare. The potential benefits of the integration of mental and physical health are increasingly recognized in patients with long-term conditions. For example, Cambridgeshire and Peterborough Clinical Commissioning Group estimated that introducing IAPT services to diabetes, cardiovascular, and respiratory pathways saved £193,000 between October 2016 and September 2017 due to reduced A&E attendances, fewer hospital admissions, and a reduction in the number of GP appointments used. Further evaluation and research into these services will clearly be beneficial (Gammie, 2017).

Conclusion

This chapter has provided an overview of the development of old age liaison psychiatry, including some of the current service models in liaison psychiatry, and common conditions seen by old age liaison teams. It has considered the advantages of having liaison psychiatry services integrated within the general hospital, the importance of detection of psychiatric illnesses, and the additional roles of the liaison team within the general hospital setting, e.g. teaching, training, and joint governance. Significant expansion of liaison services has occurred over recent years,

and the importance of liaison psychiatry is reported nationally. Much progress has been made towards recognizing old age liaison psychiatry as a subspecialty and it is increasingly recognized as being a key service as the majority of inpatients in the general hospital setting are over the age of 65. Moreover, much of the current evidence of cost savings relates to those over the age of 65.

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Social care

Chapter: Social care

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Introduction

Social care is the personal care and support required by some people because of needs arising from their age, illness, disability, or other circumstances. Support is provided in residential and nursing homes, people's own homes, and in other community settings (Wenzel et al., 2018). Outside the United Kingdom (UK), it is more frequent to see this provision described as 'social services' or 'long-term care'. Another term, 'social protection', encompasses the totality of support for older people and working-age people with disabilities, including pensions and welfare benefits, health care, and social care.

Old age psychiatrists need to understand social care because so many of their patients and their families will also be in touch with social care services. The effects of dementia and depression, in particular, are such that the overwhelming majority of patients and carers need some social care support, especially when symptoms worsen. This is clearly

demonstrated by the over-representation of people with dementia and/or depression in home care services (Pickett et al., 2012; Bruce et al., 2015; O'Brien et al., 2017) and in care homes (Prince et al., 2014; Stewart et al., 2014). At the same time, it is often only through contact with old age psychiatry services that many patients and families become aware of what kinds of social care support are available. Old age psychiatrists are also, therefore, often the first point of call for patients and their families attempting to negotiate a complicated and diverse system of social care funding and support. This highlights the importance of their role as an important link between other health and social care services.

This chapter describes the key legislation underpinning publicly funded social care, explains how it is funded, summarizes key research on personal budgets, home care, day care, and care homes, and discusses some of the key current policy debates. Social care is what is termed a 'devolved matter', so the Scottish and Welsh governments and the Northern Ireland Assembly can make their own decisions about how social care services operate under their jurisdiction. Since devolution, social care policy has become increasingly divergent across the UK. However, the overwhelming majority of social care research emanates from England, so although this chapter refers to developments in Scotland, Wales, and Northern Ireland, most of the material included is about England. It should also be noted that the volume of social care research specifically about older people with mental health problems remains limited—indeed, it is only comparatively recently that local councils began reporting data on the number of people with dementia using their services to NHS Digital. The text will make it clear when reference is made specifically to older people with mental health problems, all people aged 65 and over, and people using adult social care services as a whole.

Social care legislation

Care Act 2014

The key piece of legislation in England is the Care Act 2014, which marks one of the most significant changes to social care law in England since the National Assistance Act 1948. It was enacted alongside accompanying guidance, which has since been updated to take account of regulatory changes and feedback from stakeholders and the care sector (Department of Health and Social Care, 2018).

As well as simplifying the complex and piecemeal arrangements by which older people and people with disabilities were deemed eligible (or not) for publicly funded social care, the Act has three key principles. The first is the duty it places on councils with social services responsibilities (known as CSSRS to distinguish them from district councils which are not responsible for social care) to promote the wellbeing of adults and carers and carers in need of support living in their area. Wellbeing is defined as

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relating to any of the following, without any attempt to create a hierarchy within them:

- personal dignity (including treatment of the individual with respect);
- physical and mental health and emotional wellbeing;
- protection from abuse and neglect;
- control by the individual over day-to-day life (including over care and support, or support, provided to the individual and the way in which it is provided);
- participation in work, education, training, or recreation;
- social and economic wellbeing;
- domestic, family, and personal relationships;
- suitability of living accommodation;
- the individual's contribution to society.

Some commentators (e.g. Penfold, 2017) have suggested that this principle is the most important aspect of the Act as it underpins efforts to achieve more personalized care and support in line with the preferences of an individual, and not at the convenience of the system.

A second duty placed on local authorities is to contribute to the prevention or delay in the need for support. The increased emphasis on timely diagnosis in dementia (Dhedhi et al., 2014) and the risks of untreated depression (Briggs et al., 2018) highlight the potential for preventive support for older people and family carers. However, many carers and older people regularly report difficulties in finding out about what social care support is available and what are their entitlements (Mukadam et al., 2011; Moriarty et al., 2015). For this reason, the Care Act places a duty on local authorities to establish and maintain information and advice services in their area relating to care and support for adults and support for carers. The voluntary organization Independent Age commissioned research to see whether this new requirement had improved local councils' information and advice services, including undertaking a 'mystery shopping' exercise in which callers telephoned local councils using pre-scripted scenarios, such as asking about handrails. The report concluded that, although most information and advice services complied with the requirements of the Act, less than a third provided all the online information required by the legislation (Qa Research, 2016).

The Care Act 2014 guidance (Department of Health and Social Care, 2018) describes the assessment and eligibility process as one of the most important elements of the care and support system. People may approach a local authority for an assessment, or be referred by a third party. Local authorities then have a duty to provide assessments for any adult, including carers, appearing to have a need for care or support, regardless of the local authority's view of the level of that need or the individual's

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financial resources. This may be carried out by a person working for the local authority—or, as is happening more frequently, responsibility is delegated to another organization—for instance, to a carers' organization. The emphasis on support for carers highlights another important intention behind the Act. In the words of Norman Lamb, Minister of State for Community and Social Care during the passage of the Care Act, it would put carers on a 'level footing with those for whom they care' (Lamb, 2013).

Where an adult refuses a needs assessment, the local authority concerned is not required to carry out the assessment. However, it must go ahead with the assessment if the adult lacks capacity to refuse the assessment and the authority is satisfied that carrying out the assessment would be in the adult's best interests, or the adult is experiencing, or is at risk of, abuse or neglect. In the same way, should an individual be unable to request an assessment or struggle to express their needs during an assessment, the local authority must use the principles outlined in the Mental Capacity Act 2005 to help people be as involved as possible in their assessment and to help them make decisions about their preferred options.

Authorities also have a duty to improve the quality of care and support for adults and support for carers (including the outcomes that are achieved from such provision). Since the 1990s, local authorities have contracted with private companies and voluntary organizations to provide social care services. However, many social care providers have become increasingly dissatisfied with the level of fees paid by local councils to provide services for their residents on their behalf. In some instances, this has led some companies to withdraw from contracts with councils (Asthana, 2016). In others, it has led to cost cutting. The health and social care regulator, the Care Quality Commission (CQC), produces an annual assessment of health and social care services in England. In 2016–2017, it reported that 19% of social care services were rated as 'requires improvement'. While 78% were rated as 'good', just 2% were outstanding. This compared with 6% of National Health Service (NHS) acute hospital and mental health care services and 4% of GP practices that received the same outstanding rating (Care Quality Commission, 2017).

Social care funding

Unlike the NHS, which is free at the point of delivery, social care is means tested. Local councils currently use a combination of central government grants, local taxation, and charging for services to pay for social care. At the time of writing, people in England and Northern Ireland with assets of over £23,250 are expected to pay the full costs of the social care they receive. If their assets are between £14,250–23,250, they will be eligible for maximum financial support from their local authority but are still likely to have to make contributions from their income until they have 'spent down' to £14,250. In Scotland, the equivalent amounts are £27,250 and £17,000 (Care Information Scotland, 2018). Another key difference is

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that people in Scotland with assets of more than £27,250 who are assessed as needing personal care are not charged for this support, although they do pay for other aspects of their care, such as care home accommodation costs, day care, and meals services. In Wales, the Welsh Government has set a limit on the amount that local councils can charge for services (currently £80 per week) and has raised the amount of capital a person can keep without having to pay for their residential care to £40,000. Their intention is to eventually raise the limit to £50,000 (Welsh Government, 2018).

Crucially, across all four UK countries, housing assets are not currently included in financial assessments for social care services provided to people living in the community. Once a person moves into a care home, the situation is changed. However, councils must 'disregard' the value of a property if it is also the main residence of a carer or another close relative aged 60 and over or with a severe disability that incapacitates them. As old age psychiatrists will know, decisions about selling a family home to pay for care can lead to convoluted disputes, especially where a person is thought to have deliberately disposed (or has been deprived by others) of assets to increase eligibility for local authority funding or where families disagree about what is best for the person needing care.

Many older people are what is termed 'asset rich and income poor'. Local councils across England are expected to help those who own their own homes meet their care costs by allowing them to make 'deferred payments'. The system varies slightly across the UK but deferred payments are essentially a legal agreement whereby local councils make payments on people's behalf until they decide to sell their home or die. The proceeds from the sale are then used to repay the council. In practice, local authorities sometimes set limits on the percentage of a home's value that can be used for deferred payments. This is to prevent falls in house prices leading to a person's assets becoming less than the sum spent paying for their social care.

It has always proved difficult to get definitive figures on the proportion of people funding their own social care. Estimates suggest that about 20–25% of people using home care and 44% of residents in care homes in England are self-funding (Baxter and Glendinning, 2014) but only about a quarter of those in Welsh care homes are self-funding (Jones et al., 2016). As well as those who fully fund their own social care or whose care is fully funded by their local council, a third group consists of care home residents whose fees are partly or fully paid by their local council but who have family or friends or receive a charitable grant to pay top-up fees. These sums were originally intended to be voluntary payments for 'extras' such as a larger room or a nicer view but are increasingly used to cover the gap between the upper limit that a local council is prepared to pay for care and the actual fees charged by the care home itself (Passingham et al., 2013). Age UK estimates that about 50,000 of the 400,000 people (a figure which also includes those aged under 65) living in care homes in England are paying top-up fees. Age UK, along with other older persons

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charities, e.g. Independent Age, has described these fees as a ‘stealth tax’ with relatives often feeling pressurized into accepting them without necessarily seeing evidence of an additional service being provided.

Old age psychiatrists will know from their conversations with patients and their families that the current system in which there is no limit to the amount of money an individual might pay to fund their own social care during their lifetime accounts for much of the unhappiness with current funding arrangements. While the majority of older people only move into a care home for the final few months of their lives, leaving their assets largely intact, people with severe dementia may spend several years living in a care home. Care home fees vary throughout the country, but a person living in a nursing home specializing in dementia care could easily pay over £1,000 per week at current prices. Should that person survive for several years, they may end up using all their assets to pay for care. This is sometimes called ‘catastrophic costs’. Families and people with dementia and organizations advocating on their behalf point out that older people with, for example, cancer but not dementia are unlikely to face similar costs. The striking figure produced for the Dementia UK Update report (Prince et al., 2014) is that, while local councils pay £4.4 billion a year on social care support for people with dementia, individuals with dementia and their families are paying £5.8 billion a year on privately funded social care. This sum excludes the costs needed to replace the unpaid care provided by family and friends.

Reforming social care funding in England

There is now much greater media and public interest in social care funding than in the past—as witnessed by the furore over the so-called ‘dementia tax’ in the 2017 General Election (Heaven, 2017)—but in reality, concern about the system dates back at least to the early 1990s. This occurred when a loophole in the benefits system allowed people to claim for the cost of residential care. The result was a rapid rise in the number of people living in care homes far in excess of the growth in the number of older people in the population (Lewis and Glennerster, 1996). Faced with spiralling increases in the social security budget, the government decided to make local councils responsible for assessing people’s needs for support and for funding the care costs of people they assessed as needing support whose assets were below the limit entitling them to receive publicly funded social care. Prior to this, local councils had exercised much greater discretion in deciding what social care services they would provide and how they would assess local residents’ entitlements to support.

Since the 1990s, the gap between demand for social care and social care funding has widened considerably. There are several reasons for this. The first is the growth in the number of people aged 80 and over in the population alongside an increase in the number of people of all ages living with complex conditions. As more people live with increasingly complex needs, they require more social care support in the form of help

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with personal care, meal preparation, and other activities of daily living. In 2014–2015, approximately 578,000 people aged 65 and over were accessing long-term social care support in England, compared with 291,000 people aged 18–64. However, £6.675 billion was spent on the 18–64 age group compared with £6.927 billion on those aged 65 and over. Total expenditure on publicly funded adult social care in 2016/17 was £16.8 billion (NHS Digital, 2017). It is difficult to set this figure in an international context because countries take different approaches to defining and reporting social care expenditure (Robertson et al., 2014).

The second factor is reductions in central government grants to local authorities. For some years, councils sought to cover this gap by increasing efficiency costs and tightening eligibility criteria so that fewer people qualified for publicly funded social care support. However, between 2010 and 2020, core funding from national government will have reduced by £16 billion (Local Government Association, 2017). At one point, the 2015 Conservative government intended that these core grants would be phased out completely. Instead, councils would be allowed to retain almost of the money they raised through business rates. Many local councils argued that this change would benefit councils that raise large sums in business rates each year, e.g. Westminster, but that councils in poorer areas yielding low business rates would struggle unless there was some sort of redistribution. At the time of writing, it is not clear whether central government grants will be withdrawn completely, as originally intended (Hetherington, 2017). However, if they are withdrawn, the consequences for social care funding could be serious as adult social care constitutes the biggest area of discretionary spend for local authorities (Cromarty, 2018) and many councils report that they can only provide statutory social care services, with no leeway to develop preventative services or provide support to anyone but the most severely disabled.

The third, and final, reason for the social care funding gap is the increase in care costs. Social care is a labour-intensive but poorly remunerated service and increases in the number of people requiring intensive support mean that labour costs will also increase, even if individual earnings remain largely unchanged. As labour costs account for 50% of the cost of running a nursing home (Wanless, 2006), even comparatively small increases in wages overheads can have a considerable effect on running costs. For many years, local councils and social care providers achieved savings by controlling labour costs (Moriarty, 2015). This meant that social care was among the lowest-paid occupations. While social care workers have benefited from the introduction of the National Minimum Wage and the National Living Wage, some employers have become notorious for not paying home care workers for travel time between clients, meaning that they are illegally paid less than the National Living Wage (Gardiner and Hussein, 2015). It is also worth pointing out that although social care is a 24/7 service, enhanced payments for working unsocial hours are minimal or non-existent, which can make it especially difficult to recruit people to work in the evenings or at night. Low wages

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are universally believed to be one of the main factors contributing to longstanding difficulties in social care recruitment and retention (Moriarty et al., 2018).

The social care sector argues that, despite the action it has taken to control expenditure, this is no longer enough to cover reductions in social care funding. The Health Foundation has estimated that the funding gap for social care in 2017/2018 was at least £2bn (Health Foundation, 2017). This is projected to rise to £6bn by 2031 (Wenzel et al., 2018). Commentators are increasingly concerned that more people who need care are not having their care needs met. There is also evidence that care providers are facing quality challenges and the care provider market is becoming increasingly precarious. Furthermore, in some areas a lack of suitable care provision is adding to pressures in the health service (Cromarty, 2018).

Successive governments would argue that they have not been oblivious to what is increasingly termed a social care crisis. As the health and social care policy analyst Richard Humphries has pointed out, there have been at least five independent reviews of social care funding and twelve white papers, green papers, and consultations of one kind or another under five governments over the past 20 years (Humphries, Undated). The nearest that any government came to reforming social care funding was a commitment in the Care Act 2014 to set a means tested cap on the costs that individuals might be expected to pay for social care over their lifetime, as recommended by the Dilnot Commission (Commission on Funding of Care and Support, 2011). However, successive delays in implementing the care cap mean that this proposal has almost certainly been abandoned.

At the time of writing, the 2017 Conservative government has promised a social care Green Paper to be published in late 2018. While it is not yet known what it will propose, it is likely to consider some, if not all, of the following options. These include:

- A 'social care premium', a dedicated fund paid by those aged over 40 to fund personal care free at the point of delivery (House of Commons Health and Social Care and Housing, 2018);
- 'Prefunded social care' whereby working-age people would contribute a percentage of their income into a privately managed fund (Vasilev, 2017);
- A National Care Service, along the lines of the NHS paid for through general taxation;
- A long-term care insurance system similar to systems in countries such as Germany, Austria, Japan, and Luxembourg (Glendinning and Wills, 2018);
- Hypothecation—the earmarking of a tax to be spent on health and social care (Murray, 2018).

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In theory, private insurance products are another way of helping people insure themselves against future care costs. In practice, few are available and they are expensive. The average cost of an immediate needs annuity, usually taken out by people about to enter a care home, which pays all future fees in return for a lump sum payment, is £69,000 (Wenzel et al., 2018)—many older people are likely to decide that they are not worth the risk. Equity release is another mechanism that allows older home owners to release money from the value of their house but this is a better solution for people wanting to pay for care at home or make adaptations to their house because equity release policies usually stipulate that the sale of the house will be triggered if the policyholder(s) move into a care home. Either way, these two options are only available to a minority of older people and would not resolve the question of how to fund social care for people with severe disabilities aged 65 and under who are rarely able to build up substantial savings or housing assets.

Every proposal for reforming social care funding has its advocates and detractors. A further difficulty for policymakers is the low level of understanding among the general public about how social care is funded (Bottery et al., 2018) and a reluctance to interfere with what is seen as the 'right' to an inheritance. Sir David Behan, the Chief Executive of the CQC 2012–2018, has commented:

The future of the social care system is one of the greatest unresolved public policy issues of our time—a long-term sustainable solution is urgently required (Behan, cited in Marsh, 2017).

Only time will tell if wholesale reform to social care funding is enacted or if variants on the current system, with all its associated problems, will continue.

Personal budgets and direct payments

Personal budgets in social care are sums of money allocated by a local authority to people assessed as needing social care to be spent on services to meet their care needs. They can be managed on behalf of users by the authority, or a third party, or given to users as direct payments to spend themselves (House of Commons Committee of Public Accounts, 2017, p. 4). In Scotland, a direct payment is known as self-directed support while elsewhere in Europe, they are often term 'cash for care' payments. Direct payments in social care date back to 1997 when the Community Care (Direct Payments) Act 1996 came into force.

Until the last quarter of the twentieth century, the majority of social care services were directly provided by the state and choice was not an important factor in how they were organized. However, from the late 1970s, choice of provider has been the main way in which successive governments have sought to improve service quality (Stevens et al., 2011). In the UK, as in the majority of the more developed countries, the option for people using services to choose either social care services

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directly provided to them or to receive cash to be used to purchase services themselves has become an important policy objective, with direct payments increasingly becoming successive governments' preferred method for supporting people eligible for publicly funded social care (Ettelt et al., 2018).

[Personal budgets] are all about making the financial aspect of ... care more explicit at the individual level. By specifying the individual's budget, and allowing the individual to decide how it should be spent, the personal budget (theoretically) offers more choice, control and flexibility to the budget holder. It also places a duty on the individual to identify and potentially source the most appropriate services, and to varying degrees, manage the budget and be accountable for how it is spent (Gadsby, 2013).

Adults eligible for NHS Continuing Healthcare and children in receipt of continuing care have had a right to have a personal health budget since October 2014. Both the 2015 and 2017 Conservative governments intend that the right to a personal health budget should become more widespread.

The introduction of direct payments was particularly welcomed by members of the disability movement, mainly consisting of people aged 18–65 with physical disabilities, for whom choice was an important way of achieving greater independence and autonomy (Stevens et al., 2011). More recently, a more critical discourse has emerged highlighting the anomalies in aspirations about choice and control in a system which is actually determined by eligibility (Slasberg and Beresford, 2017) or the practicalities in dismantling some of the professional and structural barriers that exist (Ettelt et al., 2018).

This more critical discourse is informed by results from studies carried out with different groups of service users, particularly those for whom concepts such as choice and control might be less important than other aspects of care or those who may lack capacity to exercise choice and control. A randomized multimethod comparison group study compared 510 direct payment recipients (termed individual budget holders) living in 13 pilot authorities with 449 people receiving conventional services in the same locality. Its overall conclusions were that individual budgets produced positive outcomes in terms of service users' quality of life and sense of control. Benefits could also be seen for carers, who reported a better quality of life and more opportunities for a social life. However, it also reported that older people were less likely than their younger counterparts to use innovative support and were more anxious about the process of planning and managing their individual budgets. It recommended that more work is needed on tailoring approaches to the needs of different groups of service users (Manthorpe et al., 2009; Moran et al., 2011; Stevens et al., 2011; Netten et al., 2012).

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The uptake of direct payments among older people (Woolham and Benton, 2013) and among older people with mental health problems in particular, has lagged behind other groups and still remains relatively low. The original legislation excluded people with dementia but, where a person lacks capacity to manage a direct payment, it is now possible for the payment to be made to a 'suitable person' who purchases and manages care and support services on behalf of the person with dementia. A suitable person does not have to be related to the person with dementia, although in practice he or she is likely to be providing regular support. An alternative arrangement is for an Individual Service Fund (ISF), which is a managed account held by a third party who arranges for support to be provided in line with the person's wishes. They are sometimes seen as a middle way between direct payments and support arranged by the local council for people who do not have anyone who could act as a 'suitable person' or who do not want the responsibility of managing a direct payment.

Three qualitative studies (Kinnaird, 2010; Manthorpe and Samsi, 2013; Laybourne et al., 2014) have highlighted the barriers operating against direct payments for people with dementia, including practitioners' low expectations about what people with dementia would want other than conventional home care (Laybourne et al., 2014) and concerns about financial abuse (Manthorpe and Samsi, 2013). For people with dementia (Kinnaird, 2010) and 'suitable persons' (Laybourne et al., 2014), the most frequently reported problems were negotiating the social care system and practical problems such as delays in receiving the payments. At the same time, people with dementia (Kinnaird, 2010) and carers (Laybourne et al., 2014) spoke positively about the choices they were able to make, including booking a holiday cottage rather than a short break in a care home.

Home care

Home care is the main community care service supporting people with dementia living at home. It helps delay entry into long-term care for people with dementia (Andrew et al., 2000) and home care users experience better quality of life than those living in care homes (Nikmat et al., 2013). Unfortunately, there is also plenty of evidence that much home care provision is of poor quality and does not meet the needs of people with dementia. A good example of this is the practice of commissioning very short visits, sometimes as short as 15 minutes. Many people with dementia can continue to get up or prepare meals if they are given extra time and encouragement. However, this is not possible when workers need to leave quickly for their next visit. The end result is that workers may try to save time by, for example, dressing a person with dementia rather than encouraging him or her to do it independently.

Many home care workers have limited training and knowledge about dementia. Recruitment and retention problems are longstanding (Moriarty et al., 2018), which means people with dementia do not always

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benefit from having regular workers, even though continuity of care is especially important for them. Finally, almost all home care is commercially provided and changes in ownership can mean that an agency that formerly provided reliable well-trained workers no longer does so. A solution to these problems has been to set up specialist dementia home care agencies, but these are not always available everywhere.

Day services

Day services are a long-established way of providing social activities for people with dementia at the same time as giving those people who have a family carer a break. They are also valued by many older people without dementia, particularly those experiencing social isolation and loneliness (Orellana, 2018). The advent of personalization has been accompanied by the closure of many day centres, leading Needham (2013) to argue that the personalization narrative has been much more effective in legitimizing their closure than in stimulating the emergence of new collective spaces.

Day care has been shown to improve quality of life for people with dementia and reduce distressing behaviours. It may also delay placement in a care home among those cared for by adult children, although for spouses, it may act as a transitional service between community settings and living in a care home. However, conflicting findings have also been reported, accentuated by methodological challenges such as lack of differentiation between a service used for a couple of hours a week and one used every day, or differences in the types of activities that are provided and whether or not any supplementary services, such as counselling for carers, are provided (Fields et al., 2012). An important factor in one comparative study of Norwegian and Scottish day services highlighted that many of the people with dementia and their carers described an initial reluctance to use the service which changed to enjoyment as they became used to the service. The authors (Rokstad et al., 2017) argued that practitioners needed to become better at introducing the service to people with dementia and their families and explaining that feelings of apprehension were frequent and might change.

Care homes

In the UK, the term 'care home' refers to all residential long-term care settings that provide communal living and personal and/or nursing care for older people and other adults. In the past a distinction was made between residential homes providing personal care and nursing homes providing nursing care. Homes now register as a care home only or care home with nursing. These slightly unwieldy terms reflect the reality in which residents have an average at least three or more conditions (Goodman, 2016). For many years, erratic and inequitable access to specialist health care meant that residents did not always receive optimal

treatment for these conditions but there is now greater emphasis on services working together to improve this (Goodman, 2016).

Homes can also choose to specialize in providing certain types of care, such as specialist dementia care or palliative/end-of-life care. In England, residential care is overwhelmingly provided by the independent sector, with voluntary organizations providing almost all the rest. There are proportionally slightly more local authority-run homes in Scotland, Wales, and Northern Ireland, especially in places where there are fewer self-funders and profit margins are likely to be lower.

Around three-quarters of people in care homes have dementia, while just over a quarter have depression. In specialist care homes for older people with mental health problems, these proportions rise to 91% and 29%, respectively (Stewart et al., 2014). There is also evidence of significant levels of comorbidity of depression and dementia (Sutcliffe et al., 2007).

The complex health conditions experienced by many care home residents mean that a well-trained work force is essential. Despite this, levels of training among care home staff are very variable (Denning and Milne, 2009). In particular, while there has been a considerable increase in training resources for care home staff on delivering more person-centred dementia care, comparatively little of this material has been systematically evaluated for its quality and accuracy (Fossey et al., 2014).

Most of the research interventions developed in care homes are addressed at the most common problems faced by care home staff and residents (Centre for Policy on Ageing, 2014), for example, dealing with depression and dementia (Kuske et al., 2007), distressing behaviour (Moniz-Cook et al., 2017), communication skills (Moriarty et al., 2010), end-of-life care (Moriarty et al., 2012), or are aimed at areas where deficits in care are often reported, such as a shortage of activities for residents (Mozley et al., 2007). These generally report positive findings—albeit usually more in terms of staff satisfaction than improved outcomes for residents—but a key problem continues to be maintaining this training in the ‘real world’ once the intervention is over.

Other social care support

For reasons of space, it is not possible to discuss other types of social care support in more detail beyond highlighting the increasing numbers of older people with mental health problems living in supported and extra care housing (Fendt-Newlin et al., 2016) and the potential (and barriers) to the use of assistive technology (Woolham et al., 2018).

It is also worth mentioning alternative forms of social care support that tend to be on a smaller scale and not available elsewhere. These include:

- Befriending (Greenwood et al., 2016);

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- Shared Lives as an alternative to traditional day care or short breaks, whereby a person with dementia spends time in the family home of a paid worker, sometimes known as adult fostering (Shared Lives, 2017); and
- Homeshare, where a person provides low-level support and companionship to a person with dementia living at home in return for an affordable place to live (Macmillan et al., 2018).

All these services tend to be very positively evaluated by people with dementia and their carers, but it has proved difficult to ensure that they become 'standard' services available to all those who would like these forms of support.

Partnership working

Good support for older people with mental health problems requires good partnership working between health and social care. The differing origins of health and social care and different ways in which services have been organized and funded has created barriers to more effective working. However, there are policy pressures for greater integration between health and social care. The 8 Pillars of Integrated Community Support developed by Alzheimer Scotland aim to improve coordinated working for people with dementia living in the community (Blake Stevenson Ltd, 2012). The pillars are:

- A Dementia Practice Co-ordinator; (a named, skilled practitioner such as a community psychiatric nurse, social worker, or allied health professional;
- Therapeutic interventions to tackle the symptoms of the illness;
- General health care and treatment;
- Mental health care and treatment;
- Personalized support;
- Support for carers;
- Environment-adaptations and aids to support the independence of the person with dementia and assist the carer; and,
- Community connections-support to maintain social networks for both the person with dementia and the carer.

These eight pillars sum up what good social care for older people with mental health problems *should* involve, even if they are more aspirational than available across the country.

Conclusion

This chapter has tried to show the breadth of the different types of social care support available to older people with mental health problems. Many older people with mental health problems are living with other conditions and the range of challenges they face and the diversity among this group

mean that a range of social care support will be needed, especially as their growth in numbers has led to tightening eligibility criteria and reductions in the number of people who qualify for social care support (Fernandez et al., 2013).

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Care homes for older people

Chapter: Care homes for older people

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Introduction

This chapter is in three parts. First, we discuss the care home sector, looking at the changing nature of care homes and how care is provided, paid for, and regulated to achieve acceptable standards of quality. In the second part, we consider the people who live in care homes, with particular reference to their physical and mental health. Finally, we explore a positive care culture, its key dimensions, and what enhances quality of care; also, which external issues contribute to its promotion. Much of the following description of care home provision is based on the UK, but we draw from international research findings, as issues of long-term care are critical for many other countries, too.

The care home sector

Care homes in the UK

Care homes for older people

Care homes are an important sector of care provision and constitute a significant part of the general economy, with a total current value of around £15.9 billion. There are currently nearly 12,000 registered care homes for older people providing over 400,000 beds (Laing and Buisson, 2016). Of these, 261,000 beds (58%) were in establishments registered as 'care homes with nursing' (nursing homes) with the remaining 192,000 (42%) in residential care homes (without nursing). Residents receiving nursing care account for 45% of *all* care home places. Residential care homes provide 24-hour support and staff are available to help with personal care and activities of daily living, e.g. mealtimes, continence promotion, and the wellbeing, security, and safety of residents. Community nursing arrangements may be needed for individual residents (e.g. regular injections, treatment of leg ulcers). Nursing homes offer 24-hour medical care from qualified nurses. If a person's needs are best met in a nursing home and the person is eligible for NHS-funded nursing care, the costs of this are met by the relevant clinical commissioning group in England and in Wales by the local health board (Laing and Buisson, 2016).

Over the past 30 years, care home services have transformed from being a predominantly public sector activity to a predominantly private sector activity. In 2015, 90% of residential and nursing care services were delivered by independent, mainly for-profit, providers (Laing and Buisson, 2016). Until relatively recently, some NHS hospitals offered continuing care for a small proportion of very frail older people, including those with severe dementia. Now nearly all 'continuing care' patients are placed in nursing homes; a few of these are NHS run, although usually the NHS just commissions provision from private nursing homes (Lievesley et al., 2011).

Dementia is the largest specialist segment of the care home market. In 2014, an estimated 172,000 care home residents in the UK were receiving 'dementia care' whether in dedicated units or not. About 40% of all care home funding is spent on dementia care.

Currently, about 60% of capacity is operated by larger providers (with three or more care homes). The ten largest for-profit providers hold 25% of the market. Although occasionally large providers (e.g. Southern Cross) fail, it is likely that further consolidation of the market will continue. Care homes range in size from about ten beds to over 100 beds. The size of homes has approximately doubled in the last 25 years: the mean for nursing homes is now 51 places, compared to 28 for residential homes. There is a trend towards residential care homes re-registering as nursing homes where they can capture a wider pool of demand. The average occupancy rate across all homes is over 90%.

Standards of physical amenities in care homes have improved significantly in the last 20 years in response to self-pay market forces and demands from local authority commissioners. Most for-profit care homes provide single room accommodation with en suite facilities. Rooms are

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larger too, with most being at least 12 square metres; many developers build rooms larger than this to 'future proof' their assets (Health and Social Care Information Centre, 2014).

Supply side issues

Care homes are distributed unevenly across the country: there is a larger supply of places in the north of England than in south east, especially London. This pattern reflects differences in the price of housing, wage costs and income levels; different local authority and NHS commissioning practices also contribute (Humphries et al., 2016). A shortage of specialist dementia care across the UK, particularly in south east England, is a persistent concern (MacDonald and Cooper, 2007).

At present, the care home sector is contracting somewhat, with independent care home closures outweighing new places opening (Laing and Buisson, 2016). Forty-seven care home operators became insolvent in 2014/15; up from 40 in 2013/14. Care home closures are apparently due to the combined impact of market uncertainty; cuts to adult social care spending; and changes in care delivery, with greater emphasis on community-based living for frail older people (Leyland et. al., 2016).

These trends conceal wide regional variations; for example, reduction in care home beds ranges from 18% in London to 2% in the east of England. As care markets are hyperlocal, this is a significant problem for affected local authorities, older people and their families. Most care homes serve a catchment area of less than 10 miles in diameter and often rely heavily for referrals from one local authority (Laing and Buisson, 2016). Another factor relates to who pays for the bed; the care home market is highly polarized. Providers with mainly self-funding residents are relatively financially secure, while those relying on public funding are vulnerable to cuts to local authority budgets, increased costs e.g. introduction of the National Living Wage (discussed below), and financial losses (Laing and Buisson, 2016).

There are significant concerns about the future supply of care homes. It is estimated that 42,000 additional beds are needed by 2022 across England to meet the predicted demand (Bone et al., 2018). However, 87% (130 out of 150) of local authorities will probably *not* have sufficient places to meet this demand, so any additional beds will be provided by care homes catering for self-funding residents, thus amplifying the existing inequities. Despite the policy emphasis on community-based living, the complex needs profile of care home residents limits the capacity of non-residential alternatives, such as extra care housing (see section **Extra care housing**), to prevent or delay the need for it.

Relocation

An alarming consequence of care home closure is the enforced relocation of residents. Evidence suggests that relocations that are approached in a thoughtful and organized way lead to better outcomes for residents.

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Conversely, relocations which are rushed and unplanned, without actively involving residents and their families, are associated with negative outcomes including emotional distress, increased risk of depression and worsening of dementia symptoms (Jolley et al., 2011). Relocation may even increase the risk of death (Veale, 2012).

Leyland et al. (2016) found that an evidence-informed protocol on enforced relocations helped to reduce the risk of harm to residents. The protocol adopted several core principles: involving the resident and their families throughout; discussing their preferences at an early stage; and ensuring effective and timely communication about decisions, the timings of key events and the older person's rights. In addition to best practice protocols, there are several freely accessible, evidence-informed national resources (e.g. Social Care Institute for Excellence and Association of Directors of Adult Social Services, 2011). However, it appears that best practice is still not consistently applied by local authorities (Holder and Jolley, 2012). As care home closures will continue or even increase, effective management of the relocation of vulnerable older residents remains an important issue.

Extra care housing

Extra care housing (ECH) refers to accommodation with self-contained housing units, 24-hr staff on site, with domestic care and communal facilities available to residents (Evans, 2009). In 2014 there were approximately 40,000 Extra Care units in England mostly in the socially rented sector (Laing and Buisson, 2016).

Most ECH schemes offer a range of graduated support services titrated to meet dependency needs as they increase. As a model it appears to work well for those with physical disabilities and/or mild dementia (Callaghan and Towers, 2014). It is less clear how well ECH can support people with more advanced dementia and/or multiple needs and whether it delays admission to long term care for these groups (Bäumker et al., 2010). There is little development of co-housing schemes in the UK, a model of inter-generational 'shared' housing that is popular in other parts of Europe particularly Scandinavia.

Although limited in scope there is evidence that 'all forms' of retirement-related housing bring health and quality of life gains, including improvements in wellbeing following a move into the housing facility. It is also linked with reduced need for care services in the medium term and an enhanced sense of security (Netten et al., 2011; Westwood and Daly, 2016).

The hope, in the early 2000's, that ECH would offer a viable alternative to care homes, has not been realized. In a climate of financial austerity, investment in ECH provision is unlikely if decision-makers are focused on short term cost savings, and partners—housing, health, social services, and ECH providers—are not incentivized to work together. It remains to

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be seen how effective private sector retirement housing schemes are in terms of extending community-based living for older people with complex needs and delaying, or even preventing, care home admission.

Funding and paying for care

The financing of long-term care is a major concern worldwide. In England, there is an historical distinction between ‘nursing care’—paid for by the NHS—and ‘personal care’—means tested and partially or wholly paid for by the individual. This division remains highly contested and a source of widespread confusion and geographical inequity. It is further complicated as a person may be deemed eligible for NHS funding if their needs are regarded as ‘primarily health related’. This distinction is not made in Scotland where, under the Community Care and Health (Scotland) Act 2002, all long-term care is state funded.

Supporting an individual in long-term care is expensive for both the individual and the state. In the UK, the average weekly charge is around £600 per week in residential care, rising to about £840 per week in nursing homes (Laing and Buisson, 2016). The highest rates, are in the southeast of England and the lowest are in the north of England and Wales (Featherstone and Whitham, 2010). The standard rate for NHS-funded nursing care (for residents who need nursing input but do not receive NHS continuing care funding) has recently been increased, in recognition of the complex needs and high levels of dependency of many residents.

Over half of care home residents are self-funded, either in whole or part; most of the rest are fully or partially funded by their local authority, and 7% by the NHS ((Baxter and Glendinning, 2015; Laing and Buisson, 2016). The number of self-funding residents is slowly increasing as larger numbers of older people are home owners, whilst the number of wholly local authority funded residents is decreasing. In 2013–14, local authorities spent £5 billion on care home placements for older people; about a third of their overall spend on adult social care (Health and Social Care Information Centre, 2014).

The number of residents who receive NHS continuing care funding has increased in recent years, from 14,000 older people in 2005 to 43,500 in 2014. This reflects the impact of three factors: the complex health profiles of those admitted to a care home, i.e. more people are deemed to have a ‘primary health care need’; relaxation of the eligibility criteria due to an Ombudsman’s ruling in 2007; and the adversarial activities of middle-aged sons and daughters to ensure their parent is assessed appropriately for NHS funding.

Self-funding

As might be expected, there is a greater proportion of self-funders in affluent areas of England, e.g. 54% in the southern home counties, compared to 16% in Northern Ireland (Bäumker and Netten, 2011). There

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is also considerable regional variation in top-up fees, in terms both of the proportion of people being charged and the weekly amount paid. Top-up payments range from £25 pw to over £100 pw (Laing and Buisson, 2016). There is concern about when, and in what circumstances, top-ups are required (National Audit Office, 2011). Despite official guidance clearly stating that older people must have a choice of home that is ‘affordable within their budget’, independent investigations have revealed many situations where top-ups have been *expected* rather than *voluntary* (Passingham et al., 2013; Local Government Ombudsman, 2015). Such situations include: pressure placed on families at the point of hospital discharge; care home fees raised so it’s ‘pay up or move out’; and top-ups being demanded by the care home when self-funders run out of money, i.e. they reach the current threshold of £23,250¹ (in England) when they qualify for local authority funding (Ray and Sullivan, 2016).

The Local Government Ombudsman’s (2015) investigation referred to earlier also identified other relevant shortcomings. Local authorities offered inadequate information about care homes in their area to the public, and failed to take responsibility either for setting up top-up fee arrangements or to signpost relatives to independent advice about top-up fees. Care homes often charged top-up fees without notifying the local authority. Older people’s finances were sometimes assessed ahead of any assessment of their needs. Following the investigation, local authorities were told to comply with legislative guidance linked to the Care Act 2014 for England and the Social Services and Well Being Act 2015 for Wales. This includes ensuring that choice of an affordable care home is always offered and that comprehensive, accessible information—including about costs and fees—is provided to anyone who may need to place a relative in a care home.

Self-funders often pay significantly higher fees for similar services and amenities than those funded by the local authority. Self-funders are effectively cross-subsidizing publicly funded residents (Office of Fair Trading, 2005). The size of the gap between the two fee rates has been increasing over the last five years. Local authority negotiated rates are estimated to be at least £104 below the ‘floor level’ costs of keeping an older person in a care home (Laing and Buisson, 2016). Laing and Buisson found that 96% of self-funders paid more than local authorities for the same type of room in the same home, the average level of this premium being 43%. Care homes increasingly rely on this cross-subsidy to generate sufficient income (Forder and Fernandez, 2011; Jarrett, 2017).

Funding for long-term care is increasingly complex and inequitable in the UK and successive governments have failed to address it coherently. This continues to be the case.

Regulation and registration

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All care homes in the UK have to be registered with the independent regulator of health and social care services. In England this is the Care Quality Commission (CQC). Corresponding agencies in the rest of the UK are: the Care and Social Services Inspectorate Wales, the Social Care and Social Work Improvement Scotland, and the Regulation and Quality Improvement Authority in Northern Ireland.

The regulatory framework in England is discussed here by way of example. Recent years have witnessed several changes of legislation, regulator, regulatory standards, and inspection regimes. The CQC was established in 2009 by the Health and Social Care Act 2008, replacing its predecessor, the Commission for Social Care Inspection. Its responsibilities cover both health and social care services, that is, both hospitals and care homes. It originally aimed to simplify the regulatory regime, with fewer requirements for providers to meet and fewer on-site inspections, especially for providers achieving high standards. The stated aim of these changes was to create a system which was more focused on outcomes, more proportionate to risk, less burdensome, and less expensive to operate.

From 2010, the CQC used a set of Essential Standards. However, these were abandoned following two high profile abuse scandals: Winterbourne View—a private hospital for people with learning disabilities where widespread abuse was exposed—and the Mid Staffordshire NHS Foundation Trust—where 1200 unnecessary deaths occurred amidst evidence of poor care for vulnerable elderly patients (Francis Report, 2013). The CQC was heavily criticized for failing to prevent or respond appropriately to these scandals. Sir Robert Francis QC (who chaired the inquiry into the Mid Staffordshire NHS Trust scandal) regarded the Essential Standards as part of the problem; describing them as ‘over bureaucratic and failing to separate clearly what is absolutely essential from what is merely desirable’ (Francis, 2013). This led to the replacement of the Essential Standards with a set of Fundamental Standards in October of 2014 (Box 26.1).

Box 26.1 Care Quality Commission Fundamental Standards

The fundamental standards are the standards below which care must never fall:

- Person-centred care
- Dignity and respect
- Consent
- Safety
- Safeguarding from abuse
- Food and drink

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- Premises and equipment
- Complaints
- Good governance
- Staffing
- Fit and proper staff
- Duty of candour
- Display of [CQC] ratings

The CQC also revised its soft touch ‘hands off’ approach to inspection, and now seeks to visit *every service* at least once a year with a particular focus on those that present the highest risk. There are also stronger enforcement powers; directors of care companies have become more accountable for service failures; the director of a care company needs to be a ‘fit and proper person’; and there is more emphasis on good governance. However, it continues to be the case that there are no prescriptive standards on room size or staffing ratios.

Sanctions for poor performance include embargoes on local authority placements and, in extreme cases, regulators can close a service down. If care homes fail to achieve the standards required of them, they may be subject to enforcement powers by the regulator. Potential actions include:

- Using requirement notices or warning notices to set out what improvements the care provider must make and by when;
- Making changes to a care provider’s registration to limit what they may do, for example, by imposing conditions for a given time;
- Placing a provider in special measures, where they are closely supervised to help them improve within set timescales; and
- Issuing cautions or fines or prosecuting the provider where people are harmed or placed in danger (CQC, 2015).

In 2014/15, inspectors successfully prosecuted five care home providers and another 1000 had enforcement action taken against them (CQC, 2015). In 2016, the CQC also identified 37% of care homes as ‘failing on safety’ (CQC, 2016).

The CQC produces ratings of homes on a scale from outstanding to inadequate. In 2017, only 50% were rated good or outstanding with only a handful being in the latter category. On average, for-profit homes performed less well than not-for-profit or public sector homes; and independently owned for-profit homes performed better than for-profit group-owned homes. Smaller care homes (one to ten beds) received higher quality care ratings than medium or large care homes (CQC, 2017). Overall, people received poorer quality care in nursing homes; for example, in 2016, 4% of nursing homes were judged inadequate,

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compared with 2% of residential homes, and 37% of nursing homes were rated as 'requiring improvement', compared with 24% of residential care homes. Homes that catered for people with dementia were little different from those which did not (48% vs 50% rated as 'good' or 'outstanding') (CQC, 2016).

In addition to monitoring standards of quality and safety, the CQC is also responsible for assessing the financial health of adult social care providers (DH, 2016). In 2017, the CQC described social care services as 'at full stretch', and also warned that budgetary constraints—and expectations created by the Care Act—would make it challenging for providers to balance good quality of care and financial viability (CQC, 2017). Considering these pressures, the CQC noted that most care homes perform well. The costs of operating a care home are rising because of the need for a higher resident/staff ratio to care for residents with higher levels of dependency, the National Living Wage, and the increased costs of fuel, food, and other commodities.

Consumer satisfaction

Alongside ratings by external regulatory agencies, evidence from older residents themselves and their families makes an important contribution to the evaluation of care (Ray and Sullivan, 2016). Various types of survey can be undertaken, though the simplest are very short patient-related outcome and experience measures, such as the R-outcomes, howRu, and howRwe (Benson et al., 2010).

Evidence suggests that the majority of publicly funded care home residents are 'satisfied' or 'very satisfied' with their care; but no data are available on self-funders (NHS Digital, 2015). A survey looking of the experiences of care home residents reported that most felt they had more control over their lives in the care home than they had expected; their quality of life had improved compared with when they moved in; their health needs were better met than before; they were socializing as much or more than they used to; they saw their friends and relatives as much or more than they used to; and their experience of being in a care home was 'good' (Darton, 2011).

Studies of relatives of people in care homes reveal some perennial areas of dissatisfaction: the laundry services, smell, and cleaning regimes are frequent areas of concern. Communication is also an issue, particularly when the home does not keep relatives informed and when the phone is left unanswered (Ray and Sullivan, 2016). What matters to relatives is the quality of personal care and the quality of the home's management, including supervision of staff. A key worker system is regarded as important, too. For relatives, the most important issue regarding the physical environment is the accessibility of the home to wheelchair and walking aid users. Relatives also expect to be kept informed and value the

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opportunity to make comments about the home, care standards, staff, and other services (Ray and Sullivan, 2016).

A recent report (Healthwatch, 2017) based on interviews with residents, relatives, and staff at 197 care homes found that most care was fairly good. They identified several key themes:

- Quality of care varies between homes but also within the same home, with too few homes getting 'the basics' right;
- Good care homes meet all residents' health and care needs, working seamlessly with other services when residents need additional support;
- The best residential services are those that focus on enabling people to continue living as if they were still in their own homes.

Thus, the key to delivering care that responds to an individual's needs is continually to seek and act on the views of residents. This is essential to making a care home feel like an actual home.

Care home workforce

As mentioned previously, care homes constitute a substantial sector of the health and social care economy. There were around 305,000 staff employed in residential homes and 290,000 in nursing homes in England in 2017 (includes all care homes for adults, not just older people) (Skills for Care, 2017). About two-thirds are front-line staff; the rest are managers, domestic staff, administrative staff, and workers in ancillary roles, e.g. maintenance (Skills for Care, 2017).

Over half are employed on a full-time basis; just under 10% are on zero-hour contracts. In nursing homes, a higher number of staff work in a 'regulated profession', predominantly nursing (Skills for Care, 2017). Staff turnover is high, with numbers showing over a quarter of staff in 2016/17. Turnover of qualified nurses was especially high at 32%. The overall vacancy rate was 8.4%; consequently, care homes often rely on agency staff who cost two to three times as much as employees (Jarrett, 2017). Turnover and vacancy rates vary across the country; London and southeast England have particular difficulties. There is a serious shortage of care home managers: a limited cadre of skilled, experienced, and competent staff willing to take on the complex and challenging role of running a care home (Hussein and Manthorpe, 2005). The manager is often the single individual upon whom operators depend to deliver profitable services of an adequate quality.

The number of jobs in care homes has increased between 2009 and 2016, although the overall number of homes has decreased. This suggests a consolidation in the sector whereby a similar amount of care is being delivered at fewer locations, but also staffing ratios have increased in response to increased dependency levels of residents (Skills for Care, 2017). Care homes are only legally required to provide sufficient numbers

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of 'suitably trained and capable staff' to meet the needs of their residents and no ratio is specified in official guidance.

The care home sector relies heavily on low-paid staff, usually women employed part-time and paid by the hour. In 2017, 83% of the care home workforce was female (Skills for Care, 2017). Care staff are often paid close to the National Living Wage (NLW). Staffing costs can be expected to rise more rapidly in the future driven by regulation, the NLW, and the strengthening economy.

Care homes are often dependent on migrant staff, particularly in areas with staff shortages, e.g. London and the South-East (Lievesley et al., 2011). In 2014, 150,000 migrant care workers were estimated to work in care homes in England (Franklin and Brancati, 2015). Compared with their UK counterparts, migrant care workers tend to be younger and more highly skilled and qualified. Migrant workers predominantly come to the UK from India, Poland, the Philippines, Romania, and Nigeria. Potential changes to immigration policy resulting from the UK leaving the European Union could have serious consequences for the care home workforce (Franklin and Brancati, 2015).

Training for care home staff is an important issue and is discussed in the section on Training later in this chapter.

People who live in care homes

The care home population

As mentioned in the first section, there are over 400,000 older people residing in UK care homes (Laing and Buisson, 2016), which represents 4% of the population aged 65 years and older (Comas-Herrera, et al., 2011). Although the proportion of older people living in a care home at any one time is relatively small, the *lifetime* risk of needing residential care is considerable—probably about one person in five will live in a care home towards the end of their life.

As might be expected, the chance of being admitted to a home increases with age: for the age group 65–74, 0.6% of the population resides in care homes, compared with 16.7% of those aged 85 and older (Laing and Buisson, 2016). The majority of care home residents are women aged 85 years or over: most have multiple health problems, have previously lived alone, are single, widowed, or divorced, and are poor or dependent solely on benefits (Bharucha et al., 2004; Milne, 2016). Factors that protect against admission are: availability of family and formal support, adequate income, home ownership, and living in a housing environment that is adapted to accommodate disability (Denning and Milne, 2011; Milne, 2016; Westwood and Daley, 2016).

Although the UK is in a period of accelerated population ageing, with the 85+ age group expanding more rapidly than ever before, fewer older people were admitted to care homes in 2015 than in 2005 (Humphries et

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al., 2016). The proportion of male residents has increased in recent years: in 2011 there were around 2.8 female residents for each male resident, compared to a ratio of 3.3 female to male in 2001. Also, the care home population is getting older; in 2011 people aged 85 and older represented 59.2% of all residents, compared to 56.5% in 2001 (Office for National Statistics, 2014).

Older people are likely to move into a care home at a later stage in their life-course and illness trajectory than they did in the past. This pattern is influenced by several factors: personal preference of the older person to remain in their own home, a widely held negative perception of care homes as the place of 'last resort', policy emphasis on family- and community-based care, and, more recently, cuts to social care budgets (Demos, 2014). At the point of admission, residents often have complex comorbid conditions and unpredictable clinical trajectories (Forder and Caiels, 2011; Quince, 2013). Residents have become markedly more dependent over time (Lievesley et al., 2011). It has been estimated that 80% of care home residents have dementia and/or a hearing impairment, are in receipt of seven or more medications, and a significant proportion live with depression, mobility problems, pain, and/or incontinence (Cohen-Mansfield and Taylor, 2004; Laing and Buisson, 2016).

Census data from 2011 suggest that about 17,000 ethnic minority older people reside in care home in England and Wales (Office of National Statistics, 2011; Centre for Policy on Ageing, 2013). Factors within black and minority ethnic (BME) communities that may lower the rate of care home admission include: later diagnosis of dementia and/or other mental health problems due (in part) to high levels of stigma linked to mental illness; limited or no language to describe dementia; and reluctance to seek help from 'mental health' services (Milne and Smith, 2015). In general, BME residents are more likely to be male, have higher rates of dementia and incontinence, and are more dependent on admission than their white counterparts (Milne and Smith, 2015). It is important to acknowledge that 'race' and ethnicity' are contested terms and that the ethnic profile of the UK's 'minority groups' is increasingly diverse. There are growing numbers of more recently settled older people from Eastern Europe, Russia, Italy, Greece, and France, as well as those from more established populations, including South Asia and the West Indies.

Residents' health

Frailty

Frailty is a distinctive health state related to the ageing process in which multiple body systems gradually lose their in-built reserves (Turner and Clegg, 2014). Frailty is strongly related to age: up to half of all people aged 85 and older have frailty, compared to about 10% of those aged 65 and older. Older people with frailty are at risk of unpredictable deterioration in their health resulting from minor stressor events. In turn,

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this leads to increased risk of falls, disability, long-term care, and death (Clegg et al., 2013).

Frailty was traditionally used in a loose and potentially pejorative way to refer to older people with all kinds of chronic health condition. Over the last two decades, the term has become more sharply defined in terms of physiological reserve and resilience. There are two main contrasting approaches to defining frailty, known as the phenotype and cumulative deficit models. Fried and colleagues (2001) defined frailty as a phenotype characterized by unintentional weight loss (ten pounds in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity. The frailty phenotype, having three or more of these features, was an independent predictor of several adverse outcomes, ranging from falls to death. This led the authors to suggest that frailty was distinct from comorbidity (which acted as a risk factor for frailty) and disability (which arose as a consequence). In contrast, Rockwood and colleagues (2005) developed a model based on the burden created by accumulating deficits (*symptoms*, e.g. tremor and hearing loss, and *disorders*, e.g. arthritis or dementia), from which a Frailty Index was derived.

The two models have reasonable, but not perfect, agreement (Rockwood et al., 2007), and there are a number of differences between how they operate and their clinical utility (Cesari et al., 2014). The phenotype model is based strongly on physical characteristics, especially muscle strength and locomotor activity, so it does not take into account other types of impairment, most importantly cognitive impairment. It adopts a categorical approach to frailty—people are frail, pre-frail, or robust. Its advocates emphasize the consistency of the frailty syndrome and how its five components have a cyclical relationship, meaning that the process can start at any point, e.g. weight loss leading to sarcopenia, or muscle weakness leading to loss of activity, etc. (Xue, 2011).

In contrast, the cumulative deficits model is more flexible as it can take into account any type of pathology or impairment. It regards disability as a contributor to frailty, not as its consequence. The Frailty Index is a continuous variable and it is more sensitive to change over time than the phenotype criteria. The features of each model influence when and where they can be used. The phenotype model does not require a preceding clinical assessment, so it is appropriate to use at an early stage or to assess people who may be at risk. Also, it does not provide information as to the underlying cause of its features. The Frailty Index, in contrast, requires a full clinical assessment, ideally a comprehensive geriatric assessment (CGA). It can be cumbersome as the full checklist includes around 70 items. Once a score has been derived, though, it can be repeated over time for monitoring purposes.

Not surprisingly, there have been attempts to resolve the differences between these approaches or improve the shortcomings of each. These have included trying to unify them into a common scale or developing

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new scales that may have elements of each. In a comparative review, Dent and colleagues (2016) found more than 13 scales to include. As cognitive impairment and dementia are strongly associated with frailty, it has been suggested that cognitive impairment should be regarded as integral to the frailty syndrome (Avila-Funes et al., 2009; Kulmala et al., 2014).

Shorter and more convenient methods for assessing frailty are needed, particularly for use in primary care, where CGA is not readily available (Clegg et al., 2013). Numerous briefer tools have been developed to screen for frailty in in-patient settings (see Warnier et al., 2016 for a review). Brief tools are relatively sensitive but tend to lack specificity (Clegg et al., 2015). The Clinical Frailty Scale (Rockwood et al., 2005, see Fig. 11.1 in Chapter 11) is a seven-point scale derived from the Frailty Index, and it was used in the Canadian Study of Health and Aging. The British Geriatrics Society has produced recommendations for simple means to detect frailty in community and outpatient settings (Turner and Clegg, 2014). These emphasize that any contacts between health staff and older people present an opportunity. Indications of frailty from a basic assessment include: a gait speed <0.8 metres per second; a timed-up-and-go test >10 seconds; and a score of ≥ 3 on the PRISMA 7 questionnaire (Raïche et al., 2008). In addition, the common clinical presentations of frailty (falls, delirium, sudden immobility, and non-specific symptoms like fatigue) can also be used to indicate the possible presence of frailty.

Interventions that have been studied to improve or prevent frailty include exercise, nutrition, pharmacological approaches, and CGA (Clegg et al., 2013). Several systematic reviews (e.g. de Labra et al., 2015) have found modest benefits for exercise, especially for multicomponent interventions and resistance training, though the nature of the ideal programme is still unclear. CGA, including medication review, can be beneficial as it addresses each of the conditions that may be contributing to disability. Prescribed drug side effects may include sedation, loss of appetite, postural hypotension, or effects on muscle function, any of which can contribute to the frailty syndrome. Evidence that nutritional interventions improve frailty is currently lacking.

Frailty is obviously an issue in care homes. Reported prevalences of frailty in care home residents vary wildly, from 19 to 76% in one review (Kojima, 2015), which suggests marked differences in methodologies between studies. There are a number of approaches to assessing frailty in care settings. Some of these rely on the Minimum Data Set (MDS) as mandated in North America, for example the MDS-CHESS scale (Hirdes et al., 2003), which is a composite measure addressing Changes in Health, End-stage disease, and Symptoms and Signs of medical problems. It has been found to be a strong predictor of mortality, independent of other variables such as age, sex, cognition, and do-not-resuscitate orders. Clegg and colleagues (2016) developed an electronic frailty index that can be derived from routine primary care data, though its use is probably intended mainly for people living in their own homes. Another approach is

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the FRAIL-NH screening tool (Fatigue, Resistance, Ambulation, Incontinence, Loss of weight, Nutritional approach, and Help with dressing) (Kaehr et al., 2016). Each item is scored 0, 1, or 2, according to increasing deficit, apart from weight loss which is either 0 or 1, thus giving a total score out of 13. In comparison to the Frailty Index, both were significant predictors of falls and mortality, with the FRAIL-NH obviously being quicker to complete (Theou et al., 2016) and most of the required information is routinely recorded within the MDS (Luo et al., 2015). A third method is to use a measure derived from commonly used laboratory blood results combined with blood pressure measurements to construct an objective index of frailty (FI-LAB) (Rockwood et al., 2015), which was highly correlated with a clinically derived frailty measure and also a strong predictor of mortality.

It remains unclear as to what benefits might be expected by residents once they are identified as having frailty as opposed to assuming that all residents are either frail or at risk of becoming so. However, as frailty is a risk factor for other problems such as falls and delirium, it seems sensible to make them a priority for any exercise or other interventions. Frailty is not necessarily associated with lower self-rated quality of life among care home residents, either before or after adjusting for other variables, including health-related ones (Fougère et al., 2016). Siddiqi and colleagues (2016) completed a feasibility trial of an intervention (Stop Delirium!) to prevent delirium and had encouraging results even though the trial was not designed or powered to look for differences between treatment groups. Walker and colleagues (2016) reported similar results from a falls intervention feasibility trial; however, it is clear that full commitment from care home managers is required for trials to recruit to plan. Clearly in both areas, definitive trials are needed. It is also worth noting that frailty may be a barrier to the success of other types of intervention, e.g. Ellard and colleagues (2014) found that a high proportion of residents were unable to participate in a trial of exercise to combat depression, and this was a large factor in the negative result of the trial. Any intervention needs to consider carefully what residents may and may not be capable of doing.

Dementia

The prevalence of dementia in care homes is high and probably has increased in recent years. For example, Matthews and Denning (2002) reported a prevalence of 62% from data obtained in 1991–93 but Gordon and colleagues (2014) found that of a sample of 291 residents in 16 homes, 75% had a Mini Mental State Examination (MMSE) score of 22 or lower (though only 62% actually had a diagnosis of dementia). Quince (2013) considered that 80% was a reasonable estimate based on recent research. The prevalence of dementia is fairly consistent across different types of care home, though Gordon found that nursing home residents had a slightly lower mean MMSE than those in residential homes. Alongside frailty, therefore, dementia care is undoubtedly one of the principal functions of long-term care for older people: in total, there must

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be nearly 250,000 residents with dementia in UK care homes. With the cost of care home residents at around £800 per week (Romeo et al., 2016)—almost all due to care home fees—this means that care home provision is worth around £10 billion per annum.

The presence of dementia is not always diagnosed (e.g. Cheng et al., 2012). There may be various reasons for not detecting and/or not diagnosing dementia. These may include comorbidity, where the dementia can be overlooked by the severity of other conditions; insidious onset of dementia over the time the person lives in the care home; or staff attitudes towards dementia (Macdonald and Woods, 2005). Nonetheless, care home residents with dementia known to mental health services are about twice as likely to have dementia recorded on their death certificates (Perera et al., 2016), which probably reflects an increased importance of recording the diagnosis. Family carers quite often appear to be unaware that their relative has dementia, especially if they have been in the care home for a longer period (Penders et al., 2015). Helping relatives to realize that dementia is a condition that causes death has been shown to contribute to better patient comfort at the end of life (van der Steen et al., 2013), so communication with families about dementia is clearly of practical significance (see also Hennings et al., 2013).

Many residents with dementia have behaviour disturbances (or behavioural and psychological symptoms of dementia; BPSD), especially activity disturbances (agitation), aggression, psychosis, and depressed mood. The median reported prevalence of such behaviour problems in a systematic review was 78% (Seitz et al., 2010). Perhaps of particular concern are self-harming behaviours, which may be active, such as scratching oneself or punching objects (de Jonghe-Rouleau et al., 2005), or passive, e.g. refusal to take food or drink (Draper et al., 2003). Overall, behaviour problems such as agitation and aggression are commoner in severe dementia and tend to persist, as does apathy, whereas affective symptoms such as depression resolve, become less marked, or are simply not recognized (Selbaek et al., 2014; Wetzels et al., 2010). The relationship between dementia severity and types of BPSD is not straightforward. The underlying mechanisms and predictive factors are incompletely understood (Serra et al., 2010; Proitsi et al., 2011) in terms of how they relate directly to neurodegeneration or to what extent they should be viewed as attempts at communication.

Subjective quality of life is not necessarily impaired by the progression of dementia in a care home. Self-ratings of quality of life are usually higher than those made by staff (Gräske et al., 2012); such ratings are affected by depression (Hoe et al., 2006, 2009); and they do not necessarily decline on admission or over time (Moyle and O'Dwyer, 2012). Similarly, evidence suggests that care home admission does not hasten health-related decline or death. In a multivariate analysis, adjusted for other variables such as dementia severity, residing in a care home did not significantly affect survival (Xie et al., 2008). Indeed, as a consequence of identifying and treating hitherto unknown medical conditions and good

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nutrition, the overall health of some demented residents may improve. Furthermore, while some people with dementia are physically frail, a significant number—who tend to be admitted as a consequence of behavioural problems such as aggression and wandering—are relatively robust. For example, Magaziner and colleagues (2005) found that newly admitted nursing home residents with dementia were more physically fit and had lower rates of mortality than residents without dementia.

As regards interventions for dementia, it is usually recommended that nonpharmacological interventions for behaviour problems in dementia are considered ahead of drug treatments, as they are less likely to have serious side effects. Several reviews have examined the management of challenging behaviour, especially agitation and aggression, in dementia, with some concentrating specifically on care homes (see Livingston et al., 2014; Jutkowitz et al., 2016). Interventions based on providing individualized activities for residents are perhaps the most promising (Travers et al., 2016). The subject is discussed further in Chapter 19 of this book.

There have rightly been concerns about excessive prescribing of psychotropic drugs, especially antipsychotics, to older people with dementia in care homes. Many studies have shown high proportions of residents receiving antipsychotics, usually 25–40%. In a report for the Department of Health in England, Banerjee (2009) analysed existing data to show that approximately 180,000 people with dementia were being prescribed antipsychotics in one year, and this probably resulted in an additional 1,800 deaths and an additional 1,620 cerebrovascular adverse events.

Antipsychotics are only modestly effective in treating behavioural and psychotic symptoms in dementia. Risperidone and olanzapine are effective in reducing aggression and risperidone is effective in reducing psychotic symptoms (Ballard and Waite, 2006), but, because of the high levels of adverse events, they should only be used if there is marked risk or severe distress. Effectiveness appears to be limited in practice, too, as high levels of psychiatric symptoms persist in nursing homes despite treatment. Withdrawing patients from antipsychotics is usually well tolerated and adverse effects on behaviour are less common than might be expected (Declercq et al., 2013) although, in some cases of severe agitation, treatment may need to be recommenced. Although interventions (including educational programmes, medication review, in-reach, and multicomponent interventions) to reduce antipsychotic prescribing appear to be effective in the short term (Thompson-Coon et al., 2014), there are concerns that other types of drug, such as mood stabilizers (Maust et al., 2018) or benzodiazepines (Westbury et al., 2019), may simply be prescribed instead.

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Depression

There have been numerous studies of the prevalence of depression in care homes. A systematic review by Seitz and colleagues (2011) gave an overall median prevalence for major depression of 10% and depressive symptoms of 29%, and more recent studies have reported similar figures (e.g. Stewart et al., 2014). There is an appreciable incidence of new symptoms, e.g. Boorsma and colleagues (2012) reported incidence rates for DSM-IV depression of 13.6 per 100 person years in Dutch nursing homes and 10.2 per 100 person years in residential care homes. Depression tends to persist, with over 50% of depressed residents remaining so 12 months later (Midlöv et al., 2014). Suicidal thoughts are common (Malfent et al., 2010; Mezuk et al., 2014) but completed suicide among residents is uncommon (Murphy et al., 2015). Residents with higher depression scores also have a higher death rate (Barca et al., 2010).

Several factors have been reported as associated with depression, though these vary between different studies. Functional impairment and dementia both appear to be important independent risk factors. In addition, dysphoric symptoms are associated with other behavioural symptoms, e.g. aggression or verbally disruptive behaviour, in residents with cognitive impairment (Lindbo et al., 2017). Other associations that have been described include physical health variables, e.g. pain, dysphagia, diabetes, and heart disease; psychological variables, e.g. loneliness, neuroticism, and previous history of depression; and social variables, e.g. loss and the institutional environment. Of particular interest are features that should be easily remediable: access to the outdoors (Potter et al., 2017); participation in leisure activities (Ouyang et al., 2015); and using a hearing aid (Boorsma et al., 2012) all appear to have protective effects. Access to the outside environment should be regarded as a human right (Argyle et al., 2017), so it is scandalous that residents so infrequently have access to their homes' gardens.

As there has been more attention paid to depression in care home residents, it does appear that cases are more likely to be diagnosed and to receive treatment (Gaboda et al., 2011), though there is evidence that this is patchy, and homes serving more disadvantaged areas may provide less support for depression, especially to people from minority groups and with low education (Siegel et al., 2012). Possible depression should be considered at the time of admission (Iden et al., 2014). There is concern that care home nurses and other staff may overlook depression, though their rates of detection are in fact comparable to those of medical staff (Mitchell and Kakkadasam, 2011). Watson and colleagues (2009) compared available screening methods and found that a two-item scale, the PHQ-2 (Kroenke et al., 2003), performed best against a gold standard psychiatric interview, with a sensitivity of 0.80 and a specificity of 0.71. The Cornell Scale for Depression in Dementia is frequently used to assess for depression, but Jeon and colleagues (2015) found that in practice it had low diagnostic accuracy as nursing staff often did not have the time

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or relevant information to complete it accurately. The usefulness of the Geriatric Depression Scale is limited by the fact that it is self-completed and therefore not suitable for residents with significant cognitive impairment (Li et al., 2015). Koopmans and colleagues (2010) proposed a two-stage comprehensive assessment, first looking for associated factors and then looking to make a formal diagnosis of depression.

In treating depression, mixed approaches involving antidepressants and psychosocial interventions, often with a stepped care approach, seem most effective (e.g. Llewellyn-Jones et al., 1999; Leontjevas et al., 2013; Bosmans et al., 2014). Some single psychosocial interventions have been ineffective, e.g. guided self-care (Dozeman et al., 2011), and group exercise (Underwood et al., 2013). The main failing of these projects is most likely that many residents are too impaired to make use of the intervention (Ellard et al., 2014). A systematic review by Boyce and colleagues (2012) suggested that antidepressants may have modest effectiveness in treating depressed care home residents, though the quality of the included studies was often poor. There are concerns about antidepressant prescribing, for example, that residents who may benefit are not offered treatment (Dalby et al., 2008), or conversely, that antidepressants are prescribed for no documented indication (Harris et al., 2012). Rates of antidepressant prescribing for over 40% of residents have been reported (e.g. Westbury et al., 2019) even though evidence for the efficacy of antidepressant treatment in dementia is weak (Dudas et al., 2018).

In summary, depression remains a significant problem for care home residents. There is evidence that awareness and recognition of depression have improved, though the situation is still not ideal. Further progress will require improved detection and increased awareness of the importance of depression among care home staff (Dow et al., 2011). More research is needed to evaluate interventions that appear promising, and longitudinal studies of the incidence, persistence, and outcomes of depression are also needed.

Other mental health problems

Although dementia and depression are the commonest mental health problems in care home populations, other disorders may be present too (sleep disorders are discussed in Chapter 48). Anxiety symptoms are also common, though their severity varies, and anxiety may be symptomatic of other disorders, such as depression or physical illness. In a review of 18 studies, Creighton and colleagues (2016) found reported prevalence rates for anxiety disorders at 3–20%, though the higher quality studies were around 6%. However, this group's own study (Creighton et al., 2017b) reported a prevalence of 19% for anxiety disorders plus 12% for subthreshold disorders. Anxiety disorders are most strongly associated with health-related variables, notably depression, stroke, poor vision, pain, and lower quality of life (Smalbrugge et al., 2005; Creighton et al., 2017a). There is a lack of high-quality treatment studies for anxiety

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disorders. One study found that a stepped care approach that was effective for preventing depression did not help to prevent anxiety (Dozeman et al., 2012). Chapter 42 discusses anxiety disorders in more detail.

Although the numbers of older people with severe long-term mental illnesses, such as schizophrenia and bipolar disorder, has risen in many developed countries (see Chapter 45), they experience worse health than others people of comparable age. For example, they have higher rates of several medical disorders (notably cardiac failure and chronic pulmonary disease) and higher rates of healthcare utilization (Hendrie et al., 2013, 2014). Middle-aged and older people with schizophrenia are much more likely to move into residential and nursing home care at an earlier age than people without previous mental illness. For example, Andrews and colleagues (2009) found that rates of nursing home admission were about four times higher. This may have to do with the loss or burnout of family carers, often ageing parents, as well as decline in the person's own health and functioning. Cognitive impairment and behaviour are important predictors of nursing home as opposed to community residence. Among older patients with schizophrenia (age range 40–97), residence in assisted living facilities was also associated with never having been married, presence of cognitive impairment, and poorer quality of wellbeing (Auslander et al., 2001). Such patients often fit poorly into conventional nursing home environments, so other models of care, e.g. separate units or supported community living, may be preferable (Bartels et al., 2003). Depla and colleagues (2003) favoured a model that deployed psychiatric staff to work with care home staff, rather than having a psychiatric unit within the home or the home itself employing its own psychiatrically trained staff.

Substance misuse remains a neglected area in relation to care homes, with almost no published research in the last decade. Clearly there is some residential provision for people with alcohol and substance misuse problems, but most of these residents are not elderly. Most of what little research there is comes from Veterans Administration (VA) homes in the US, where substance misuse disorders appear to be an independent risk factor for admission (Lemke and Schaefer, 2010). Almost half of VA residents had a lifetime history of significant heavy drinking (abuse or dependence) (Joseph et al., 1995). These residents tend to be younger, male, and more likely to be of Afro-American origin, with more psychiatric comorbidity, though more independent with activities of daily living than other residents (Brennan and Greenbaum, 2005). This distinct profile leads to challenges in providing care, but also perhaps offers some potential for rehabilitation. Elsewhere, a study of over 300 residents in northern France (Leurs et al., 2010) found that two-thirds of residents drank alcohol on a daily basis and nearly 20% were heavy drinkers. Apart from these glimpses, we have very little picture of how older people with histories of substance misuse fare in care homes. Doubtless, significant quantities of alcohol are consumed, some of it covertly, and the next

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generation of care home residents will include significant numbers of people who have used recreational drugs for much of their lives.

Older people with intellectual disabilities (ID) have particular residential needs (Ward, 2012). The move of a person with ID into residential care is often a result of a social change, such as the death of a parent, rather than a change in the needs of the person him/herself. This may be associated with the double impact of a bereavement as well as loss of previous familiar surroundings. People with ID may be placed in residential care for older people at a relatively young age, which may also cause problems for them in terms of social isolation (Winkler et al., 2006) and other residents who may not understand or tolerate their needs or behaviour (Wilkinson et al., 2004). Furthermore, the staff group may be unskilled in meeting their needs. Improving the lives of older people with ID who are placed in mainstream older people's care homes requires action on several fronts. These include: ensuring that services for people with ID are better equipped to meet age-related needs; preventing people from entering older people's services that are unable to offer them an appropriate level of care and quality of life; and reviewing the appropriateness and quality of placements of all people with ID in residential and nursing homes for older people (Thompson et al., 2004).

Physical health of care home residents

Comorbidity

As already discussed, care home residents are a frail group, with high levels of physical and mental health conditions. Comorbidity is not synonymous with frailty, although the two terms overlap, since comorbidity can exist in the absence of frailty. Physical conditions, with impaired mobility seeming to be especially important, are among the most important predictors of admission to care homes (along with dementia and widowhood) (Hajek et al., 2015).

Among residents, chronic illnesses and disabilities are common, frequently with evidence of unmet need or inadequate care. Cohort studies of residents consistently describe multiple physical conditions often coexisting with mental health problems, notably depression and dementia. For example, in a survey of 16,000 residents, Bowman and colleagues (2004) found that 78% had at least one form of mental impairment, 71% were incontinent, and 76% needed help with mobility or were immobile; overall, 27% were immobile, confused, *and* incontinent. Gordon and colleagues (2014) reported a sample of over 200 residents who had a mean number of 6.2 diagnosed conditions alongside considerable cognitive and functional impairment, and were being prescribed an average of eight prescriptions each.

There have been efforts to improve the management of long-term conditions such as diabetes, helped by national guidelines such as those issued by Diabetes UK (Sinclair et al., 2011). Consequently, aspects of

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diabetic monitoring and access to services like chiropody have improved, though with some inconsistencies and definite scope to involve residents more in their own care (Yarnall et al., 2012). Cancer is also common in nursing homes. For example, almost all residents have some kind of skin lesion (Deo et al., 2015) and these include skin cancers (mainly basal cell and squamous cell carcinomas) in around one-third of residents. People living with cancer in care homes often report feelings of loneliness and loss (Drageset et al., 2015), and there is evidence that cancer pain is under-recognized and under-treated in care homes (Drageset et al., 2014). There is thus plenty of scope to improve recognition of cancer, though screening for asymptomatic cancer is not warranted (Rodin, 2017), as well as providing social support, activity, and adequate pain relief.

However, there are opportunities for improving health care for older people when they move into a care home. There should be a thorough assessment of their needs, as they will often now be registered with a new GP, which provides the chance to reappraise any long-term conditions and any treatment. This should include a review of medication, aiming to simplify it where possible. It is also important to communicate realistically with residents and their families about their expectations concerning the medical care of the older person, in particular about whether resuscitation or hospital admission are appropriate or not should an emergency arise. The physical examination of frail older people is discussed in Chapter 11. The next few sections discuss some of the more important issues, but are not intended to be fully comprehensive.

Sensory impairment

The impact of hearing loss upon cognition and dementia has been the subject of much recent attention, with studies indicating that hearing loss is a risk factor for cognitive decline and incident dementia (e.g. Lin et al., 2013). In a review, Livingston and colleagues (2017) found that hearing loss from middle age onwards almost doubled the risk of developing dementia and suggested that hearing loss contributes 9% of the population attributable factor for developing dementia (i.e. the percentage reduction in new cases that would result if the risk were eliminated). The nature of the mechanism is unclear but it is likely that a combination of factors is at work, which could include shared (presumably vascular) pathology, increased cognitive load if unable to hear properly, or social disengagement as a consequence. It remains unclear if hearing-related interventions in mid-life or later can reduce the impact upon cognition. By the time dementia has been developed, the opportunity may have been lost: for example, Allen and colleagues (2003) found that fitting hearing aids improved global ratings, but did not improve other specific outcomes, e.g. cognition, behaviour, or psychiatric symptoms.

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Given the advanced age of many care home residents, it is not surprising that the majority of residents have at least some degree of hearing loss. In the UK, this equates to at least 250,000 residents with hearing loss (Echalier, 2012). Additionally, many of these will also be living with frailty, dementia, and other health problems. Hearing loss leads to a diminished ability to communicate, which can lead to depression (Brink and Stones, 2007), feelings of being unable to connect with other people, and loss of control over the person's own life (Roets-Merken et al., 2017). Hearing loss is also associated with higher levels of behaviour problems (Hall and O'Connor, 2004; Yamada et al., 2014). Furthermore, noisy environments within care homes can exacerbate communication difficulties, especially at mealtimes or during group activities (Pryce and Gooberman-Hill, 2012).

Impairment of hearing may be easily overlooked as staff may lack knowledge and confidence about hearing problems (Solheim et al., 2016) or simply don't think they are worth doing anything about. Care assistants may find it difficult to distinguish between hearing loss and dementia as causes of impaired communication, though this improves if they know the individual residents well (Slaughter et al., 2014). Hearing assessments may need to be modified as most residents are unable to complete usual test procedures (Burkhalter et al., 2009), though screening should be possible nonetheless (Jupiter, 2012). It is important to check for the presence of impacted cerumen as this is commonly found and its removal often leads not only to improvements in hearing but also modest improvement of cognition (Moore et al., 2002).

Managing hearing loss in care homes can be challenging, for example, difficulties with residents using hearing aids because they fit poorly, don't work properly, batteries run out, and residents can't handle them, with many (86%) needing help (Cohen-Mansfield and Taylor, 2004). However, simply screening and providing hearing aids does not appear to be cost effective as the uptake is relatively poor (Linssen et al., 2013). What seems more effective is working with staff on aspects of care, for example, with the goal of increasing resident autonomy (Roets-Merken et al., 2016), but more work is needed to provide evidence of best practice (Denning et al., 2017). Echalier (2012) identified three areas for action: i) intervene earlier in hearing loss; ii) meet communication needs in care homes through staff training and a regulatory focus on communication; and iii) improve hearing aid use and management. A more recent realist review of hearing-related communication by Crosbie and colleagues (2019) highlighted five interlinked areas: i) leadership promoting positive regard and empathy through person-centred care; ii) communication training for staff; iii) 'knowing the person' and relationship building for responsive awareness of residents' hearing needs; iv) maintaining and monitoring hearing communication through care planning, including appropriate use of hearing aids; and v) managing noise in the care home environment. All of these, however, required a sense of permission from

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the care home leaders to enable staff to be knowledgeable and feeling empowered to provide good care.

Visual impairment has perhaps attracted less research than hearing impairment (for a review, see Banks and Ward, 2017) but it is evident that visual loss is present in half or more of care home residents (Lamoureux et al., 2009; Thederan et al., 2016). The nature of the problem is often unrecorded and care staff frequently appear to be unaware even of its existence (Jensen and Tubæk, 2017). Visual loss has numerous effects on a person, including disorientation, falls, potential isolation, depression, and reduced quality of life (Banks and Ward, 2017; Ward and Banks, 2017). Uptake of potential treatment, such as spectacles or cataract extraction, appears to be poor unless there are specific initiatives (e.g. Friedman et al., 2005; Marmamula et al., 2013). Again, there is a lack of evidence as to whether potential interventions are effective and, if so, what these should be. It is probable, however, that working with staff to improve their understanding and communication will turn out to be more effective than simply providing equipment or treatments.

Dual sensory impairment affecting both vision and hearing is also common, presenting in about one-third of care home residents (Yamada et al., 2014). As might be expected, it has profound consequences, e.g. being associated with depression (Guthrie et al., 2016), more behaviour problems (Yamada et al., 2015), more rapid cognitive decline (Yamada et al., 2016a), and increased mortality (Yamada et al., 2016b), especially if the impairment has led to reduced participation in activities.

Pain

Pain is common, especially from arthritis and pressure areas. Numerous studies report that half or more of care home residents have been identified as experiencing one or more painful conditions (e.g. Barry et al., 2015; Björk et al., 2016; Takai et al., 2013). Pain is associated with low mood and reduced participation in activities (Lapane et al., 2012), and with agitation and aggressive behaviour (Ahn and Horgas, 2013). Residents with dementia less frequently indicate that they are in pain and thus are sometimes not offered analgesia as frequently as those without impaired communication (Monroe et al., 2014), though this is not always the case (Tan et al., 2016). It has often been reported that pain is undertreated, but some recent studies have shown high levels of analgesic prescribing (Tan et al., 2016; Veal et al., 2014), though this is no guarantee that treatment is being administered effectively. Improved pain management may benefit the health and quality of life of residents with dementia (Husebo et al., 2011) but there is still room for improvement, which requires a more consistent approach, with standard guidelines and wider use of pain rating scales, including those with nonverbal items (such as facial expression) that can be used for patients with language impairment (for a review, see Husebo et al., 2016).

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Mobility and falls

Mobility problems are common in the care home population. Most residents have some limitation of mobility with a significant number being totally immobile. Immobility is associated with multiple other problems, such as incontinence, falls, and pressure ulcers (Lahmann et al., 2015).

The incidence of falls is high, and figures of around 10% in a year have been reported (Quigley et al., 2012), of which at least 20% have serious consequences, e.g. hip fractures, intracranial, and facial injuries. Risk factors for falls in care homes are similar to those in other settings and include impaired mobility, poor physical health, disinhibited behaviour, and medication, including antihypertensives and psychotropic drugs (Kosse et al., 2015; Kröpelin et al., 2013).

There have now been numerous trials and several systematic reviews of falls prevention programmes (Cameron et al., 2012; Choi and Hector, 2012; Lee and Kim, 2017; Vlaeyen et al., 2015). These have slightly varying interpretations but there is some consensus for multicomponent interventions that involve exercise, reducing falls in recurrent fallers. However, the best results have come from programmes that involved external input, so sustaining improvements is challenging and so far, attempts to train care staff to deliver programmes have been ineffective (Colón-Emeric et al., 2017). One criticism is that existing programmes have not involved residents sufficiently in their design and implementation (Meyer et al., 2016).

Nutrition

Concern is often expressed about poor standards of nutrition in care homes. Food may be poorly presented or unappetizing, the environment may be uncongenial, special diets (for religious observance or medical conditions) may be unavailable, and residents often have conditions, such as dysphagia or xerostomia (dry mouth), that may affect their ability to feed themselves or to swallow their food. Numerous studies have documented poor oral health among residents, with lack of teeth; high rates of decay; active symptoms, such as dental pain; and inability to clean their own teeth (e.g. Gaszynska et al., 2014; Karki et al., 2015). Overall, up to half of all care residents may have or be at risk of malnutrition (Agarwal et al., 2016). Poor nutrition adversely affects the wellbeing of residents (Muurinen et al., 2015) and poor food intake is strongly associated with various adverse outcomes, including falls, functional decline, and death (Streicher et al., 2017).

Various tools are available for assessment of nutritional status, of which the most widely used is the Mini Nutritional Assessment (MNA) (Vellas et al., 2006). Various mealtime interventions have been investigated, including changes to food service, food improvement, dining environment alteration, staff training, and feeding assistance. There is some evidence to suggest that attention to these areas can have positive effects on

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resident nutrition (Abbott et al., 2013) and behaviour in residents with dementia (Whear et al., 2014). Improving the mealtime experience is generally well received by residents (Kenkmann et al., 2010) but it may be that the goals of achieving weight gain or increased body mass index may be simply too tough given the high level of frailty in the resident population.

The use of feeding tubes (percutaneous endoscopic gastrostomy (PEG) tubes) in care home residents with dementia remains controversial, though there is no evidence of benefit (Sampson et al., 2009) or increased survival (Teno et al., 2012): indeed, at least one recent study found increased mortality (Ticinesi et al., 2016).

Death and end-of-life care

Given the advanced years and the prevalence of serious health problems among care home residents, mortality rates are bound to be high. There are however relatively few studies. Shah and colleagues (2013) used a primary care database including almost 10,000 care home residents aged 65 and older and reported that 26% died within one year, compared to 3% of the same age group in the community. McCann and colleagues (2009) found a median survival in Northern Ireland of 2.3 years for people admitted to nursing homes and 4.5 years for residential homes.

Deaths often occur in care homes, with about 20% of deaths in the UK occurring in nursing and residential homes (National Council for Palliative Care, 2006). However, about 55% of deaths of people with dementia occur in care homes (Sleeman et al., 2014), a proportion that has increased in the last decade or so. This probably reflects increasing attention to palliative and end-of-life care in dementia as well as initiatives to avoid what are seen as unnecessary admissions to hospital.

Management of dying patients in care homes, especially those with dementia, varies considerably and is often inadequate. However, under the right circumstances care homes are capable of providing a comfortable and hospice-type environment (Fleming et al., 2017). Palliative and end-of-life care are discussed in more detail in Chapter 27 and Chapter 53.

Creating a positive care culture

Much greater attention is now being paid to the experience of living in a care home. Initiatives include systematic projects such as *My Home Life* (see <http://myhomelife.org.uk/>), resident and consumer surveys, and various other accounts. For people who are frail, dependent, and living in a care home, quality of life and quality of care are intertwined (Goodman et al., 2017). Positive outcomes in this context depend to a large extent on effective day-to-day care. It is important to note that 'care' includes not only those elements provided within the home, but also external services such as medical care and social support. Furthermore, good-quality care depends on a range of micro-level (satisfied staff) and macro-level

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(financial stability of the provider) factors and their interaction; this make it a complex and multifaceted construct (Ray and Sullivan, 2016).

Moving into a care home precedes living in one, and the next section discusses this important transition.

Moving into a care home

Most people enter a care home because they can no longer live independently as a result of physical and/or mental illness. People are often very frail. Admission is usually unplanned following the death of a spouse, a domestic crisis, a breakdown in care arrangements at home or an episode of acute hospital treatment (Harrison et al., 2017). In fact, over half of the admissions to care homes come from hospital; many of these are of people with dementia (Laing and Buisson, 2016). Circumstances which are linked to unplanned hospital admissions include: falls; confusion and incontinence; chronic conditions managed in the community but where care has broken down; and/or a cycle of repeated hospital readmissions that disrupt formal and informal care arrangements (Westwood and Daly, 2016).

The death or breakdown of a family carer is a primary trigger for admission to both a care home and hospital. In the UK, Banerjee and colleagues (2003) found that having a co-resident carer at home had a strongly protective effect—the risk of being institutionalized was 20 times higher in people who did not have a carer living with them. This must be one of the most striking demonstrations of the importance of carers anywhere in the research literature. Other people's concerns and anxieties for the older person's wellbeing, safety, and protection can also be a driver (Bowers et al., 2009). The 'other people' include relatives, friends, and health and social care staff. There is a risk that their wish for a 'safe' option may sometimes override the wishes of the older person.

Transitions, especially from hospital, into a care home are managed in variable and inconsistent ways (Hanratty et al., 2014; Kable et al. 2015). It is well documented that unsupported transitions can have a negative impact on older person's wellbeing (Ellis et al. 2010; Goodman et al. 2017; Scheibl et al., 2019a). A positive transition is more likely if the older person is involved in the decision to move (Gilbert et al. 2015; Scheibl et al., 2019b) and for those living with dementia the reason for moving is explained and they are allocated a 'buddy' for the first 48 hours of their stay (Sury et al., 2013). A crucial part of the process is for the older person to find a sense of 'home'; this appears to be closely associated with wellbeing and quality of life (Tester et al., 2004; Bowers et al., 2009; Hall and Beatty, 2014).

But even when relocation is accepted the transition can still be challenging; it is a time of considerable physiological, functional, psychological, and social decompensation (Ellis et al., 2010; Sussman and Dupuis, 2014). Quite apart from the stress of giving up one's home, there

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are other losses to contend with: of friends, pets, and community attachments. Frail older people with complex needs might make several transitions as their illness progresses, amplifying the impact of these challenges. Adverse reactions, such as feeling like an 'outsider' or social disengagement, can place a person at risk of depression (Knight and Mellor, 2007).

There is often relatively little time to plan the move or to make informed choices about which home best suits the older person. There are limited guidance and/or standards in place to support good practice regarding the management of the transitions (Harrison et al., 2017). If a move to a care home is necessary, then one of the primary needs of older people and their families is for information; some excellent guidance is available, covering many of the practical and financial issues that need to be addressed (e.g. Independent Age, 2017). Publicly available information about quality of care, including care home standards, is also published by the CQC.

Most of the evidence about moving into care from older people themselves and their families is in the form of qualitative accounts. Davies and Nolan (2003, 2004, 2006) studied the experience of transition into residential care from the perspective of relatives, based on 37 interviews with 48 people who had assisted a close relative to move in. They distinguished three phases embedded in the process of transition: 'making the best of it'; 'making the move'; and 'making it better', referring to the periods before, during, and after the move. The My Home Life programme, while seeking to improve care for people living in care homes, specifically identified managing transitions as a core theme (Owen et al., 2012). It emphasized the importance of maintaining key relationships in the process of making decisions, transition, and post-transition in promoting the older person's wellbeing. Several of these themes have been discussed in the earlier section on Relocation.

Social connectedness and quality of life

The importance of supporting older people living in care homes to participate in everyday life, in order to encourage social engagement and enhance quality of life, is now well recognized (NICE, 2013). However, *feeling* socially connected is not generated simply by encouraging older people to engage in social or recreational activities (Knight and Mellor, 2007). Getting to the older person and gaining insight into their lived experience is more likely to help them to feel included (Mikelyte and Milne, 2016). This underscores the point made earlier that care home staff must be able to engage in emotional work with residents alongside their role in meeting residents' personal and physical care needs (Lee et al, 2013). Life story work may support care home staff to engage with 'the person', and building up a picture of the older person's life with family members is also important (Kellett et al., 2009).

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Obviously, an older person is more likely to feel isolated and socially disengaged if there is absence or loss of close family members and friends. The Residents and Relatives Association (2010) estimated that 13,000 care home residents had no one to visit them at all, and many more residents had family members who did not, or could not, visit for various reasons. In this context, the quality of day-to-day relationships between older residents and care workers is pivotal to quality of life.

For residents to feel truly at home, they need to be supported in various ways, e.g. expressing and retaining aspects of their identity, preserving important continuities, and being treated as an individual who is known and cared about (Bridges, 2007). Appreciation of cultural values, preferences, religious and spiritual beliefs, and personal biographies—including areas of biographical sensitivity—are crucial elements in knowing a person. Aspects of personal life, such as sexuality and intimacy, are easily side-lined in practice with older people, reinforced by persistent stereotypes and ageism (see Robinson and Molzahan, 2007; see also Chapter 50). Assuming that an older person is ‘asexual’ is to potentially deny an integral part of a person’s identity and continued desire for intimacy. Older LGBTI people have often experienced discrimination in health and social care services and may hide their sexual identity or the existence of a partner in a care home setting (Stonewall, 2011). They may need sensitive support to feel able to express their sexual identity.

Various approaches have been developed to promote social connectedness of older residents. An important example, based on relationship-centred care, is the SENSES framework developed by Nolan and colleagues (2006). This highlights the fundamental importance of relationships in care homes in supporting older residents. The six Senses in the framework (security, continuity, belonging, purpose, achievement, and significance) are described in more detail in Chapter 15. The Senses framework offers a shared language and common ground between families and care professionals, across their potential differences in assumptions, values, attitudes, and behaviours (Davies et al., 2009).

The Joseph Rowntree Foundation’s *Better Life Programme* (Bowers et al., 2009; Katz et al., 2011) identified that older people with high support needs want a quality of life that includes relationships, living somewhere pleasant and accessible, having input into decisions that affect them, and the opportunity to mix with peers and others (see Box 26.2 for the key dimensions).

Box 26.2 Dimensions of a good quality of life in a care home

- 1 People knowing and caring about you.
- 2 The importance of belonging, relationships, and links with your local or chosen communities.

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- 3 Being able to contribute to family, social, community, and communal life, and being valued for what you do.
- 4 Being treated as an equal and as an adult.
- 5 Respect for your routines and commitments.
- 6 Being able to choose how to spend your time—pursuing interests, dreams, and goals—and who you spend it with.
- 7 Having and retaining your own sense of self and personal identity—including being able to express your views and feelings.
- 8 Feeling good about your surroundings, both shared and private.
- 9 Getting out and about.

Reproduced with permission from Bowers, H., et al. Older people's vision for long-term care. Copyright © 2009, Older People's Programme, Published by Joseph Rowntree Foundation, York. <http://www.jrf.org.uk/reports>.

Research has identified some of the barriers to achieving these goals (Owen et al., 2012), which include: negative stereotypes and ageist assumptions about the capacities of older residents; dealing with the organizational requirements that take staff away from front-line caring, e.g. excessive paperwork; permitting staff to spend time with residents thus building up a relationship separately from the delivery of care tasks; providing supervision and support; and facilitating opportunities to engage residents as 'stakeholders' in the care home, not just passive recipients of care. Other findings suggest that promoting a bottom-up culture that rewards empathy and engagement in the staff team leads to higher levels of wellbeing among both residents and staff and reduces staff turnover.

Promoting good health and wellbeing

Until recently, there has little emphasis on promoting the health of care home residents, despite evidence that even among people with advanced dementia, improvements in health and wellbeing are possible (Livingston et al., 2008). For example, multifaceted interventions to reduce depression in care home residents can not only reduce or resolve symptoms, but also can improve overall quality of life and wellbeing (Lyne et al., 2006). Interventions to promote physical health among residents also show positive results for both physical and mental health (Milne, 2009).

Other areas where good practice can improve mental health outcomes include: the careful management of transition into the care home (as noted above); knowledge about the nature and needs of the older person *before* admission; regular assessment of the mental health status of residents; and an understanding that poor health is (often) amenable to

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medical and/or psychosocial intervention (Ray et al., 2009). A commitment to person-centred care in the home, with a particular focus on a biographical approach and staff spending time on developing relationships with residents, is strongly linked to the promotion of health and wellbeing (Ballard et al., 2018).

Since 2015, in England the NHS has been running an Enhanced Health in Care Homes framework as part of its Vanguard programme to develop new models of care across the health service. Six sites have participated, developing projects around interventions such as medicines management, multi-disciplinary team support (such as dementia outreach teams), and end-of-life care (NHS England, 2016). It is intended that the most successful initiatives will become widespread and commissioned across the country.

Access to health services

How well health services work with care homes and provide support to residents lies at the heart of 'good healthcare' for the care home population. Research demonstrates a long history of erratic and inequitable approaches to healthcare delivery by both primary and secondary healthcare agencies and practitioners (Goodman and Davies, 2011). Although there are examples of innovation and good practice, these tend to be time limited, discretionary, and locally determined; often they depend on an individual practitioner's interest. Care home residents have tended not to be a priority by either primary care or specialist services, with care homes effectively being regarded as 'off the radar'.

The situation has improved somewhat in recent years, due to two probable main factors: first, increased recognition of the contribution that care homes make to the spectrum of care for long-term conditions, and second, a perception that residents are often admitted 'inappropriately' to acute hospitals, with consequent high costs to the NHS. Initiatives to improve matters often consist of a genuine wish to enhance the quality of care mixed with a ruthless intent to cut costs. The Care Home Vanguard programme exemplifies both components of this mixture. Where investment is made to develop, outcomes of interest can include earlier identification of preventable illness among residents, earlier referral to specialist services, and delayed or preventable hospital admission (Goodman and Davies, 2011). So far, however, evidence that hospital admissions and healthcare costs can be reduced is generally lacking.

Consistent regular primary healthcare input to care homes is widely regarded as important by residents and care home staff. Mental health services have a specific role to play in support of care home staff and residents, though the most effective and efficient way of using specialist mental health input has yet to be adequately demonstrated (Thompson, 2011). The recently completed Optimal study (Gordon et al., 2018) used realist evaluation to investigate under what circumstances NHS health services for care homes worked effectively, and identified four context-

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mechanism-outcome configurations that underlay effective working. These were: i) investment in care home-specific work that legitimizes and values work with care homes; ii) relational working that, over time, builds trust between practitioners; iii) care that 'wraps around' care homes; and iv) access to specialist care for older people with dementia. The emphasis on relational working and care home-specific expertise suggests that time is of the essence to establish trust and openness between care staff and health professionals.

Primary care occupies a crucial place in support of care homes in the UK, but alternatives are possible, e.g. in countries like the Netherlands, where specialist elderly care physicians (Verenso, 2015) are employed to work full-time in nursing homes. There are good arguments for establishing a similar specialism in the UK (Oliver et al., 2014; Gordon, 2015).

Research

Research in care homes presents a number of challenges. First of all, many of the residents are frail and lack the capacity to give consent to participate in research. Residents' families and ethics committees have in the past taken a protectionist view towards residents, even if the residents themselves would have been willing to take part. Also, as mentioned, care homes vary in size, shape, and type and, as they are often independently owned, each home has to grant access to researchers. This is complex and time consuming. Additionally, in the past at least, there has often been no culture of research and enquiry in care homes and, for some, a sense of futility about the benefits of any studies that might be carried out. Generally speaking, care home residents have been an invisible population.

However, the last decade or so has seen more attention paid to research in this area, reflected in a marked increase in the number of funded studies and published papers. This reflects a realization that care homes are providing a significant amount of care for long-term conditions, including frailty and multimorbidity, and are a major arena for end-of-life care. Furthermore, it is increasingly recognized that they are not isolated from the rest of the health and social care system, so how they operate has implications for other providers, especially hospitals. Alongside this, in England, the Mental Capacity Act 2005 specifies the conditions under which people who lack capacity can participate in research, so that there is now a reasonable pathway to ensuring the inclusion of care home residents. More recently, the National Institute for Health Research has established the ENRICH (Enabling Research in Care Homes; see <http://enrich.nihr.ac.uk/>) network, which seeks to build links between researchers and the community of care homes (Davies et al., 2014). A growing user movement among people with dementia in research, in all settings, has also contributed to research participation (Litherland, 2015).

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ENRICH is probably the first national care home research network, though in other countries (notably the Netherlands and the US) there are often strong links between academic departments and nursing homes. Much US research on care homes uses data from the national Minimum Data Set (MDS), which means that information regarding large numbers of residents is readily accessible to researchers. The UK has no such dataset, which places many studies at the (costly) disadvantage that they have to start recruitment and collecting data from scratch; this underscores the case for establishing a UK-wide MDS (Goodman et al., 2017, p. 125). Care home research is also supported by the flourishing specialist *Journal of the American Medical Directors Association*, which has a rapidly increasing impact factor; it has relabelled itself as the *Journal of Post-Acute and Long-Term Care Medicine*, which accurately reflects its purpose.

In terms of what research should be conducted, we need to know about what constitutes good and effective care, how to promote positive health among residents despite the high prevalence of chronic conditions, and how to prepare and support staff to use best practice all of the time, for every resident. The positive role that can be played by increasing understanding of the lived experiences of residents and what constitutes a 'good quality of life' in a care home setting cannot be overstated. Clinical trials can be difficult to perform because of the high level of attrition in the frail population of residents, but observational studies and research involving staff and relatives are feasible, and this may be a good area for realist methodology, which seeks to enquire what works, for whom, and under what circumstances.

Training

Staff training is essential for improving quality of care in care homes, especially in supporting residents with dementia. While evidence strongly suggests that training makes a more sustainable difference when embedded across the whole care home and/or organization (including management and ancillary staff), much of the focus of training initiatives is front-line care staff (Loveday, 2011). There is a strong correlation between high-quality care and a well-trained workforce, particularly in dementia care. Research suggests that training can impact positively on staff attitudes, skills, knowledge, and performance; it can also result in increased confidence and higher levels of job satisfaction and retention (Wild et al., 2010; Skills for Care and Skills for Health, 2011).

In recent years, more attention has been accorded to formal training and qualifications for care staff. For example, the Care Certificate was launched in 2015, aimed at non-regulated care workers, including care home staff. Around two-thirds of direct care staff have achieved, or are working towards, the Care Certificate (Skills for Care, 2017). The most frequent areas of training received were: moving and handling, safeguarding adults, and health and safety. The Curriculum for Dementia Education (Dementia UK, 2014) includes core topics and more detailed

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items suitable for pre-registration or non-professional staff. The Health and Social Care Act 2012 removed the requirement for specific qualification standards in care homes in England, raising concerns about how training and skills will be consistently promoted. Nonetheless, national and local investment in systemic training programmes remains necessary not only to improve care, but also to increase staff retention rates, improve staff satisfaction levels, and reduce turnover (Cook et al., 2018).

Conclusion

The care home sector is complex and controversial. It supports some of the most vulnerable and frail older people in the UK, many of whom have dementia and other mental health problems. Its profile is increasingly that of a sector divided by provider type, individual capacity to self-fund and geographical variability. Although the care home population is largely invisible in many communities and in most public discourse, it is attracting greater attention than it once did from policy makers and researchers.

There are a number of issues that characterize the sector. How it will meet growing demand for its services is a dominant concern. Capacity in UK care homes fell for 12 years up to 2009. Although it has remained fairly stable since then, the number of places will need to approximately double in the next 20 years simply to maintain the current ratio of institutional to community-based care for people with dementia. By 2081 it is likely that around 1.5 million care home places will be required in the UK (Laing and Buisson, 2016). How such an increase will be funded and how the balance of funding—private vs public and local authority vs the NHS—will be managed remains largely unresolved.

This demand reflects a steady growth in the size of the very old population and a concomitant increase in the number of people with chronic disability, comorbid ill health, dementia, challenging behaviour, limited communication skills, and incontinence. Future demand for care home places will be influenced by a range of factors, including the changing but vital role that families play in supporting older relatives at home, the changing ethnic profile of the population, the costs and quality of community-based care, the role of alternative forms of long-term care (e.g. extra care housing), and the rising number of older people with substantial assets. The sector is likely to be increasingly defined by a small number of large independent providers. The need for more nursing homes, as opposed to residential care homes, will increase or, possibly, the—often false—distinction between the two will be abandoned.

Although care homes often have a ‘bad press’—and there are prominent instances of neglect and mistreatment—overall, the standard of both environment and care has improved considerably over the last 20 years. We anticipate further change resulting from better knowledge about good practice, improved medical and psychosocial support to care homes,

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greater access to training, and enlightened regulation. Perceptions about care homes should change, so that they are no longer considered the option of last refuge, but rather as valued facilities for providing kindness, care, and comfort at the end of life. We need to recognize the complex work done in care homes, and how vital their contribution is to the total picture of care for people with long-term conditions. Also needed is a greater awareness of the needs of care home residents, the potential to make an active informed choice to live in a care home, and the inclusion of care homes in community life. We hope that future work will emphasize the perspectives of residents themselves (Milne, 2011) and will invest in interventions to improve mental health and the quality of residents' lives, the quality and capacity of care home staff, and the quality of care and support residents receive.

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Notes:

1 In England to be eligible for local authority funding, an older person must have capital assets of under £23,250. Care home residents with under £23,250 in savings have to contribute all of their weekly income towards the fees, except for £23.50 per week, which they can keep to spend on personal items.



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Palliative and end-of-life care

Chapter: Palliative and end-of-life care

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The epidemiology of dying with dementia

As populations age, in the UK and other developed countries there will be a steady increase in the number of deaths, and a proportion of those will die over the age of 85 years (Gomes and Higginson, 2008). Projections of future need suggest that by 2040, annual deaths in England and Wales are projected to rise by 25.4% (from 501,424 in 2014 to 628,659) (Etkind et al., 2017). Despite the fact that most deaths occur in adults over the age of 65 years, there is widespread evidence that older people have inequitable access to good end-of-life care, and for people with mental health problems such as chronic schizophrenia or with neurodegenerative diseases such as dementia, there are further barriers to adequately meeting their needs (Davies and Higginson, 2004, Sampson et al., 2006).

Globally, about 47 million people were living with dementia in 2015, and this number is projected to triple by 2050. The prevalence of dementia increases with age, affecting 6% of those aged 75–79 years and one-third

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of people over the age of 95 (Knapp and Privette, 2007). Thus, increasing numbers of people will die with dementia. Estimates from the UK Medical Research Council–Cognitive Function and Ageing Studies (MRC–CFAS) project, a large multicentre study looking at the health and cognitive function of 13,000 older people, suggest that people who died between the ages of 65 and 69 years had a 6% risk of dying with dementia, rising to a 58% risk of dying with dementia in those over 95 years. In the UK, one in three people over the age of 65 will die with dementia (Brayne et al., 2006) and in 2015 dementia became the commonest cause of death in men and women over the age of 80 years (Office for National Statistics, 2017). Deaths due to dementia will increase from around 59,000 in 2014 to around 220,000 deaths per year by 2040, which will then lead to an increased need for palliative care (Etkind et al., 2017).

People with dementia may also have a range of other comorbidities and may be frail. Frailty is found in a quarter to a half of people over 85 years of age and is associated with increased vulnerability to physiological stressors (Clegg et al., 2013). Abellan van Kan and colleagues (2008) define frailty as ‘an aggregate expression of risk resulting from age- or disease-associated physiologic accumulation of subthreshold decrements affecting multiple physiologic systems resulting in adverse health outcomes’.

Frailty and dementia are multifactorial in origin and share some common aetiological pathways resulting from cumulative exposures over a number of years (Neale et al., 2001). Smoking, obesity, lack of physical activity, and depression have been linked to the development of both frailty and dementia (Woods et al., 2005, Ownby et al., 2006, Peters et al., 2008, Hamer and Chida, 2009). There is a temporal association between frailty and increased risk of developing cognitive impairment; furthermore, increased frailty will accelerate cognitive decline (Clegg et al., 2013). Both dementia and frailty have an adverse impact on a range of outcomes, including acute hospital admission (Mukadam and Sampson, 2011; Wagner et al., 2006) and falls (Myers et al., 1991). These outcomes are independent of physical comorbidity and other potential confounders such as age and gender (Avila-Funes et al., 2009).

Dementia and frailty are life-limiting conditions

Despite the impact that dementia and frailty have on older people and their families, they have not traditionally been conceptualized as ‘terminal’ or ‘life-limiting’ syndromes. For example, care home medical and nursing staff consistently overestimate prognosis in advanced dementia. In one study of nursing home carers and physicians, at nursing home admission only 1.1% of residents were perceived to have life-expectancy of under six months; however, 71% died within that period (Mitchell et al., 2004b). The median length of stay in UK nursing homes, where the majority of residents will have moderate or severe dementia, is 18 months. With a median survival time of 1.3 years, advanced dementia (as defined by a Functional Assessment Staging Scale (FAST) score of 7c

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and higher) is associated with a life-expectancy similar to that of well-recognized terminal diseases such as metastatic breast cancer (Mitchell et al., 2009).

A recent UK population study gave a median survival time from diagnosis of dementia to death of 4.1 years (Xie et al., 2008); this is strongly influenced by age, with those aged 65–69 years surviving for a median 10.7 years, and those aged 90 years and above surviving for 3.8 years (Xie et al., 2008). As expected, older people defined as being frail also have a significantly increased risk of death (Clegg et al., 2013).

Identifying when frail older people with dementia are reaching the end of their life can be challenging. Numerous studies have attempted to identify prognostic indicators or indices that may guide physicians to adopting a more palliative approach to care, but these tools are more reliable at identifying people with dementia at *low* risk of dying rather than those at *higher* risk of death (van der Steen et al., 2005). Clinical judgment, discussion with families and carers, and taking the opportunity to reassess or shift the goals of management towards palliative care at times of intercurrent illness or transition may be a more practical and reliable approach (van der Steen, 2010).

For example, acute physical illness requiring emergency hospital admission, such as pneumonia and urinary tract infections, may be an indicator of imminent death in people with advanced dementia (Morrison and Siu, 2000b; Mitchell et al., 2009; Sampson et al., 2009a). This population also has markedly increased six-month mortality after hip fracture (55%) and pneumonia (53%), compared to 12% and 13% in cognitively intact patients (Morrison and Siu, 2000b). Shorter-term mortality is also very high, with 24% of those with moderate or severe dementia dying after acute unplanned medical admissions, compared to 7.5% of those who did not have dementia (Sampson et al., 2009a).

However, there is little evidence that many active medical interventions, e.g. artificial hydration and nutrition, hospital admission, prolong or improve the quality of life in people with dementia (Sampson et al., 2009b; van der Steen, 2010). Additionally, there is increasing interest in how a palliative approach may be beneficial for frail older people with advanced dementia (Livingston et al., 2017).

What is palliative care?

The World Health Organization defines palliative care as:

an approach that improves the quality of life of patients and their families facing the problems associated with life threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual (Gomez-Batiste et al., 2007).

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The phrase *end-of-life care* may be used synonymously with *palliative care*, particularly in the US. Its use is favoured because palliative care is sometimes associated only with cancer, whereas end-of-life care refers to all patients with life-limiting illnesses. In European countries, end-of-life care is often used to describe the care given during the last few hours or days of life.

The European Association of Palliative Care (EAPC) published a consensus statement attempting to define the principles of practice. All definitions share a common philosophy of care, which is to take a holistic approach, valuing autonomy of patients and their families, with a focus on: dignity; a collaborative relationship between healthcare professionals, patients, and their families; good communication; and a central goal to maintain the quality of life. These are, of course, all characteristics required by professionals working in any mental health setting. It is also important to note that end-of-life care 'seeks neither to hasten death, nor to postpone it' (Radbruch et al., 2009).

For the purposes of this chapter we focus mainly on end-of-life care of older people with advanced dementia, as this is where the focus of policy, research, and clinical provision has most recently been directed.

The clinical picture of advanced dementia

There are no operationalized clinical criteria for advanced dementia, but Reisberg (1988) suggests that it can be defined as a FAST level of 7 and higher: the person with dementia (PWD) cannot dress him- or herself, is doubly incontinent, and speaks at most only a few words.

In contrast with the early and middle stages of dementia, the clinical features of advanced dementia are less well characterized and researched. People with advanced dementia suffer a range of symptoms, similar to those found in the terminal stages of cancer, e.g. pain and dyspnoea. Pressure sores, agitation, and eating problems (i.e. difficulty with swallowing or loss of appetite) are very common as the end of life approaches (see Table 27.1).

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Table 27.1 Prevalence of symptoms (percentage) in nursing home residents with advanced dementia.

Study details	Mitchell et al. (2009)	Sampson et al. (2017)	Black et al. (2006)	DiGiulio et al. (2008)	Aminoff and Adunsky (2005)	Klapwijk et al. (2014)
	Proportion with symptoms 18 months prior to death (prospective study) <i>n</i> = 323	Proportion with symptoms in the last nine months of life (prospective study) <i>n</i> = 85	Proportion of residents with life expectancy of six months (prospective study) <i>n</i> = 126	Proportion of residents in the last 30 days of life (retrospective study) <i>n</i> = 141	Proportion of residents in the last week of life (prospective study) <i>n</i> = 71	Proportion of residents in last five days of life (prospective study) <i>n</i> = 24
Dyspnoea	46	47	29	39	–	30
Pain	40	55	63	26	18	35
Pressure ulcers	39	27	61	47	70	7
Agitation/ restlessness	54	45	50	20	72	19.4
Aspiration	41	20	15	–	–	–
Eating problems/ difficulty swallowing	86	57	85	–	95	38.7

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A retrospective study comparing symptoms experienced in the last year of life by 170 people with dementia compared to 1,513 cancer patients showed that the symptom burden between the two groups was comparable; in particular, 64% of dementia patients experienced pain and 57% had loss of appetite. The healthcare needs of both groups were also similar (McCarthy et al., 1997). The careful management of these specific symptoms is vital in providing a holistic approach to end-of-life care for people with dementia.

Pain

Pain is common in people with advanced dementia and is often underdetected and undertreated (Scherder et al., 2009), particularly towards the end of life (Sampson et al., 2017; Klapwijk et al., 2014). Retrospective interviews with relatives and carers indicate that significantly more dementia patients are reported to experience pain in the last six months of life compared to those with cancer (75% vs 60%) (McCarthy et al., 1997), but pain control is often inadequate. In patients with fractured neck of femur, those with cognitive impairment were prescribed only a third as much analgesia as cognitively intact controls (Morrison and Siu, 2000a). There is no consistent evidence to suggest that pain experience is less intense, but people with advanced dementia will have difficulties in communicating that they are in pain and interpreting pain signals. This often manifests as behavioural change such as agitation, distress, social withdrawal, depression, or resistive behaviour (Scherder et al., 2009; Sampson et al., 2015).

The 'gold standard' for pain assessment is self-reporting. Despite widely held beliefs to the contrary, many patients with moderate to severe dementia can report pain reliably (Zwakhalen et al., 2006). In those with communication difficulties it may be necessary to use direct observation or validated observational pain scales such as the Abbey Tool (Abbey et al., 2004). The assessment of pain in advanced dementia is, however, complex and it has been suggested that there is no evidence that pain produces any unique features that may not be caused by other sources of distress (Regnard et al., 2003; Cohen-Mansfield et al., 2015); and thus tools such as the Disability Distress Assessment Tool (DiSDAT) may be more appropriate (Regnard et al., 2007).

Managing pain in a person with advanced dementia requires careful assessment for possible underlying causes. This should include clinical examination, observation of behaviours (both at rest and during movement), and discussion with family members or staff who know the person well. In some cases, response to a trial of analgesic may in itself be a diagnostic tool (Herr et al., 2006). The aetiology of pain may be acute and may, for example, be associated with urinary retention, constipation (Kovach et al., 2006), myocardial infarction, deep vein thrombosis, or acute infection. Common chronic causes of pain in people with advanced dementia include pressure sores, undetected fractures,

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poor dentition, awkward positioning in chair or bed, and arthritis (Davis and Srivastava, 2003).

Treating pain in this population requires a stepped approach (Abdulla et al., 2013). Depending on the cause, nonpharmacological interventions may be helpful, particularly where there is a musculoskeletal aetiology. This may include repositioning, provision of optimal seating or specialist beds, physiotherapy, massage, heat, or cold. Simple analgesia such as paracetamol and non-steroidal inflammatory drugs can be very effective. The key to achieving a good result is regular prescribing; as-required medication is often not given as people with advanced dementia may not report they are in pain or request painkillers. If simple analgesics are ineffective then stronger analgesia such as opioids should be considered. Side effects such as delirium, constipation, and sedation may occur, but in practice these can be managed. An important recent study (Husebo et al., 2011) demonstrated how this approach to the management of pain significantly reduced agitation in residents of nursing homes with moderate to severe dementia. Regular paracetamol was effective in 63% of participants, and of the 25% who received opioids only 2% had these discontinued because of side effects. The intervention also showed beneficial effects on mood (Husebo et al., 2014) and sleep (Blytt et al., 2017).

Behavioural and psychological symptoms of dementia

Behavioural and psychological symptoms of dementia (BPSD) are common in dementia, affecting 90% of people at some time during the course of their illness. They can be extremely distressing both for people with dementia and their family and carers, and they are also a strong predictor of institutionalization to nursing or residential homes (van der Linde et al., 2016). Different BPSD tend to emerge at different stages of the illness, e.g. mood disorders and depression are noted earlier in the disease course and psychotic symptoms (hallucinations and delusions) are more common in moderately severe dementia. Wandering and agitation tend to be the most enduring BPSD. In the advanced stages of dementia, over half of patients remain agitated and distressed (Sampson et al., 2017; Mitchell et al., 2009). The management of these symptoms is complex and requires a structured approach, using a range of therapeutic approaches. Difficult behaviours, e.g. aggression and resistance to care, may be indicators of unmet needs, for example, undetected or untreated pain, delirium, or infection. Therefore, a full assessment is required, which can be challenging in advanced dementia when verbal communication is limited. Basic aspects of personal care, such as providing glasses or hearing aids, should be considered first. Environmental modifications, such as limiting noise or providing outside space or gardens where people can walk, can reduce agitation. Psychological interventions, e.g. simple 'ABC' analysis (documentation of the Antecedents of the behaviour, the Behavioural disturbance, and the Consequences of the behaviour) can reveal patterns and triggers for a particular problem, and are also very effective (Kovach et al., 2006;

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Testad et al., 2010), and drugs should be used as a last resort. Antipsychotic medications both typical and atypical can cause parkinsonism, prolongation of the QT interval, and increase the risk of stroke and death (Schneider et al., 2006; Maust et al., 2015).

Eating and swallowing

People with advanced dementia often develop swallowing difficulties. Two methods of enteral tube feeding are used: a nasogastric tube (a tube that is passed through the nose and into the stomach) or via a percutaneous endoscopic gastrostomy (PEG) (directly through the abdominal wall into the stomach). Sampson and colleagues (2009b) found no randomized controlled trials of these interventions in people with advanced dementia; furthermore, the review showed inconclusive evidence that enteral tube feeding provides any benefit in terms of survival time, mortality risk, nutritional parameters, and improvement or reduced incidence of pressure ulcers. There have been no studies on the effect of these interventions on quality of life. Enteral tube feeding may increase pulmonary secretions, incontinence, mortality, and morbidity. PEG is an invasive surgical procedure with significant postoperative risks, including aspiration pneumonia, oesophageal perforation, migration of the tube, haemorrhage, and wound infection.

The decision to use enteral tube feeding is emotive and influenced by complex ethical issues, clinical need, local practice, physician and carer preference, and whether there is an advance directive or care plan in place. Clinicians may feel pressurized by institutional (Lopez et al., 2010), societal, or local laws to intervene. For example, in the US, only the state of Illinois requires a physician to seek a court order to withhold or withdraw tube feeding. Ethical considerations include whether life in advanced dementia should be artificially prolonged and what is considered to constitute 'euthanasia', i.e. the difficult issue that by withholding food and fluids death will be hastened. It has been argued that the absence of evidence demonstrating a benefit of tube feeding does not mean that it is inappropriate in all patients with advanced dementia and that each individual deserves a holistic assessment by a specialist in swallowing; all appropriate interventions should be considered, including the option of a gastrostomy (Regnard et al., 2010). Some ethicists suggest that artificial nutrition and hydration are medical treatments that can legitimately be withheld if their risks, *judged according to the patient's values*, outweigh their benefits (Gillick, 2000); however, this implies that values are known or documented and this is often not the case.

Whether 'to feed or not to feed' is perhaps not such a stark binary decision as it may seem. Modifying or thickening foods, providing finger foods, and offering alternative choices that the person likes (identified from personalized care documentation such as *This Is Me*) may improve nutrition and increase weight (Hanson et al., 2011). 'Comfort feeding' (sometimes referred to as 'risk feeding' is becoming more widely used (Palecek et al., 2010); tastes and sips of food combined with mouth

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care are used to promote comfort and pleasure, focusing on the quality of the interaction with the care giver as much as the provision of nutrition.

Infections and pneumonia

Pneumonia and other infections, especially of the urinary tract, are common in advanced dementia. Over 18 months, 53% of nursing home residents with advanced dementia will have a febrile episode, and 41% will have pneumonia (Mitchell et al., 2009) and people with dementia are more than twice as likely to die from pneumonia compared to those without (Foley et al., 2015). People with advanced dementia are often immobile, bed bound, at increased risk of aspiration, and may have impaired immunological function. The use of antibiotics to treat fevers and recurrent infections is one of the most controversial issues in this field. Fabiszewski and colleagues (1990) demonstrated no difference in mortality between people receiving antibiotics and those receiving only 'palliative' care. In a cohort of Dutch nursing home residents, van der Steen and colleagues (2002) found that those treated with antibiotics survived for longer (27% died compared to 90% of those who did not have antibiotics); however, this may have been related to the fact that antibiotics were withheld from residents whom physicians believed had more severe dementia. Some research has suggested that withholding antibiotics increases the level of discomfort (van der Steen et al., 2009), but it has also been argued that antibiotics might delay death, leaving the patient exposed to the risk of further pain and suffering and prolonging the dying phase. In this situation, adequate symptomatic control using analgesia may be more appropriate.

Care settings

Many recent national and international palliative care policies have focused on how best to provide people with the opportunity to die in a place of their choice (Department of Health, 2008). International population surveys have demonstrated how over two-thirds of people say that they would prefer to die at home (Gomes et al., 2012). However, in western populations over the last hundred years there has been a large shift away from deaths at home to deaths in hospitals and care facilities. For example, in the UK, between 1974 and 2003 the proportion of home deaths fell from 31% to 18% overall. This occurred at an even higher rate for people aged 65 and over, women, and people dying from non-cancer related causes (Gomes and Higginson, 2008). Concurrently, the proportion of older people dying in long-term care facilities such as residential and nursing homes has increased across Europe and the US, where 40% of deaths occur in long-term care facilities. In the UK there has been a trend towards decreased deaths in hospitals and increasing numbers of deaths in care homes for people with dementia (Sleeman et al., 2014).

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Care homes

When frail older people with dementia are moved to a care home, they frequently experience multiple losses: physical, mental, social, and spiritual. Although death may not necessarily be imminent, residents of care homes are highly likely to die there, making these settings where palliative care is most needed (Cartwright, 2002; Oliver et al., 2004; Froggatt et al., 2006). Several barriers may obstruct the provision of good-quality palliative care in these settings. These include high rates of staff turnover, lack of access to primary care medical support and specialist palliative care resources when required, and fear of censure by regulatory authorities if deaths occur in the care home (Denning et al., 2012). In the UK, medical support to care homes is variable and concerns have been raised when acute illness occurs at night and on-call doctors may not have the information necessary to make the decision that a resident requires palliative care and not active intervention. This can lead to the distressing situation where a resident is admitted to the acute hospital and dies there. A related issue is that of anticipatory prescribing. For example, care homes may not hold drugs, particularly opiates, which are commonly held by palliative care teams and hospices. The funding of long-term care and palliative care varies widely between different countries. In the US, there is a focus on 'hospice appropriateness', whereby Health Management Organizations will fund palliative care for people with dementia, once it has been agreed that they have a likely survival time of fewer than six months. In the Netherlands, care homes are served by specialist nursing home physicians, and therefore much palliative care is given 'in house' (Koopmans et al., 2010).

Hospices

It is often stated that people with dementia are 'denied' access to hospices; fewer than 1% of hospice patients in Europe have a neurological diagnosis (Davies and Higginson, 2004), and in the US, fewer than 7% of hospice patients have a primary diagnosis of dementia (Jennings, 2003). The reasons for this are complex and related to many of the issues described earlier, e.g. that dementia is not perceived to be a terminal illness, concerns that hospice staff will not be able to manage BPSD (McCarty and Volicer, 2009; Sanders and Swails, 2009). People with dementia are also less likely to be referred to palliative care services, and in many health systems access to hospices is dependent on recommendations from these services. It has been argued that hospices provide 'specialist' palliative care and that they should rightly focus on cases of complex need—most of the symptoms experienced by people with dementia at the end of life, such as pain and difficulties with swallowing, do not require specialist intervention but good generalist care.

Over recent years there has been a shift in hospice care and their willingness to embrace dementia. Progress was galvanized by the launch of the Hospice UK report on hospice-enabled dementia care (Hospice UK,

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2015). While this may not result in more people with dementia being admitted to and dying in hospice, many are now providing or developing community and hospice outreach services (Denning et al., 2017b).

Person-centred care and spirituality at the end of life

What it is to be a person is central to our understanding of person-centred care. Person-centred care is now a widely acknowledged basis for dementia care delivery and is a term that is synonymous with treating people as individuals, respecting their rights as a person, and (from a professional carer perspective) in building therapeutic relationships (McCormack and McCance, 2010).

Tom Kitwood, a noted leader in the movement for person-centred care in dementia, extended the concept of person-centred care (see Box 27.1) to consider personhood and the status of being a person, and developed a definition of personhood as a '... standing or status that is bestowed upon one human being by others, in the context of relationship and social being' (Kitwood, 1997). This established the concept of person-centred care within relationships with others.

Box 27.1 Key features of person-centred care

- Looks at care from the perspective of the individual.
- Acknowledges each person as a unique individual with a rich history and own memories, preferences, wishes, and needs.
- Respects the dignity, autonomy, and independence of the person with dementia.
- Focuses on the positive rather than the negative.
- Focuses on strengths and abilities rather than weaknesses and disabilities.
- Promotes wellbeing.
- Ensures care is planned around the individual, not around the care system.
- Acknowledges there is usually a reason for a behaviour, and views behaviours that challenge others as an expression of feelings and/or a means of communication.
- Accepts the reality of the person with dementia and does not insist on bringing the person into another reality that can cause distress.

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People with dementia, particularly those in the advanced stages, are reportedly often denied care that is ‘person-centred’, and Post (1990) suggests they may be classified as already ‘dead’; he states that, due to the lack of empowering capacities, people with advanced dementia may be seen as ‘nonpersons’. The ethical and philosophical debate on the concepts of self and personhood draws together the central issues of both dignity and spirituality.

Spiritual care is an important aspect of patient care and there is growing interest in spirituality and spiritual care. These have become increasingly essential components in person-centred care and quality of life of people with dementia, especially towards the end of life, when capacity may be lost. A review of spiritual care (Holloway et al., 2010) commissioned to support the implementation of the End of Life Care Strategy (Department of Health, 2008) found spirituality to be of particular concern within the nursing literature, though most material was more concerned with its assessment, rather than on specific interventions. Ensuring spiritual care is met in people with dementia is the responsibility of all members of the health and social care team (Department of Health, 2008). Fulfilling spiritual needs has a positive impact on people’s psychological and physical wellbeing (Agli et al., 2015). However, spirituality is a complex phenomenon and is not well understood by practitioners (MacKinlay and Trevitt, 2007). Thus, spiritual needs are often ignored, particularly in relation to people with dementia (Skomakerstuen Odbehr et al., 2015).

Namaste

Sensory stimulation is a form of spiritual care that requires no verbal communication. It can help foster people’s sense of connection with themselves and families/friends/caregivers (Simard and Volicer, 2010; Nicholls et al., 2013). Gentle massage of the hands, shoulder, neck, and face has been found to cause people with dementia who are normally withdrawn to reach out and touch the caregiver’s hands, face, or body, in a gesture of reciprocation (Nicholls et al., 2013). Namaste Care (Simard, 2013) is an example of a systematic, multisensory care programme that is aimed specifically at meeting the spiritual needs of people with advanced dementia who are no longer able to participate in social or group activities (‘Namaste’ means to honour the spirit within). It integrates meaningful activity with multisensory stimulation, nursing care, person-centred care, and reminiscence (Simard, 2013). It has been shown to enhance the wellbeing of people with dementia, decrease agitated behaviours, improve communication and nutritional intake, and help people and their family/loved ones to reconnect with each other (Simard and Volicer, 2010; Stacpoole et al., 2017).

Advance care planning

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The fear of not being seen as a 'whole person' or cared for in a person-centred way has contributed to the anxieties that people have about their future health. For example, when asked what health worries they were most concerned about when they got older, more people worried about developing dementia (58%) than were concerned about getting cancer (47%) or having a heart attack (47%) (Fernández and Forder, 2010). The experiences of people with dementia are starting to have a positive influence on our understanding of person-centred care from the perspective of the PWD. Based on her personal experience as a PWD, Bryden (2005) maintains that people with dementia should take the opportunities to explore with other people more existential issues about life and death, while they still retain the capacity to plan their future care.

Advance care planning (ACP) is understood in a variety of different ways. The term is often used without definition or explanation and different emphases are placed upon the different elements of the care planning (Henry and Seymour, 2007). ACP usually involves a process of discussing and recording priorities and wishes for future care and treatment between individuals and their health and/or social care providers. It attempts to anticipate the future deterioration of a person's condition so that when a person is no longer able to communicate, for whatever reason, wishes and preferences that have been recorded earlier can be met (Froggatt et al., 2008).

In contrast to those with cancer and other advanced chronic disease, people with dementia may have profound cognitive impairment and lack the capacity required to make decisions about their care and treatment. People with dementia are significantly less likely to have an ACP compared to those with cancer, although uptake of the process in cancer remains variable (Mitchell et al., 2004a). Ideally, developing an ACP should be attempted in the earlier stages of dementia when a person is still competent to make decisions. An MMSE score of 18–20 appears to be a consistent threshold score required to make an ACP (Fazel et al., 2000; Gregory et al., 2007). Below this threshold, individuals appear more likely to opt for life-sustaining treatments (Fazel et al., 2000) but as dementia progresses there is increased caregiver involvement in decision-making (Hirschman et al., 2006). In current UK clinical practice, it remains rare for a person with advanced dementia to have an ACP, while little is known about how ACP may benefit people with dementia and their carers (Denning et al., 2011).

Advance care planning and decisions about life-sustaining treatment

Professionals and family carers often anticipate an adverse reaction to pursuing ACP with the PWD, but this is not necessarily the case. Finucane and colleagues (1993) found that such concerns in family carers were unfounded, and that the PWD showed no distress either before or after ACP discussions. Carer attitudes may influence the likelihood of people with dementia being exposed to aggressive treatments at end of life. Mezey and colleagues (1996) found that carers with a greater sense of

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burden were more likely to consent to life-sustaining treatment. Fazel and colleagues (2000) found that people with dementia were more likely to make decisions that were impulsive or opt for life-sustaining interventions than controls, but Finucane and colleagues (1993) found that people with dementia were more likely to refuse life-sustaining therapy as they became more cognitively impaired.

Family carers and decision-making

Decision-making for people with dementia at the end of life may be fraught with problems, with prompts for discussions about ACP perhaps triggered by a medical event, transitions and changes to the living situation, or a hospital admission for the PWD. In the absence of any defined ACP, decision-making often falls to family carers, with increasing caregiver 'burden' being a significant predictor of caregiver-dominated decision-making (Hirschman et al., 2004). However, family carers are often unprepared to make effective decisions about end-of-life care for the PWD (Forbes et al., 2000; Denning et al., 2012).

A study of dyad interviews (a PWD and their family carer) found that, although the partners claimed to have a shared approach to decision-making, this had in fact been largely untested until the diagnosis of dementia was made (Denning et al., (2016, 2017b). Despite this lack of preparedness, carers are often called upon to support clinical decision-making at a time when the PWD no longer has the capacity to do so. Family carers found the increasing burden of assuming the day-to-day decision-making on behalf of the PWD wearisome, which meant that they did not have the emotional energy to consider medium- or long-term planning (Denning et al., 2017c). Furthermore, both PWD and carers showed marked uncertainty about end-of-life treatment choices, often reflecting that they did not have enough information about potential future health states to make such decisions. However, this meant that carers could accurately predict the PWD's preferences in the here-and-now, but, at best, were only moderately able to predict treatment choices in future hypothetical health states (Denning et al., 2016).

Professional attitudes

A priority of UK government policy is to improve the diagnosis rates of dementia (Banerjee and Owen, 2009). However, of equal importance at this time must be supporting people with dementia to consider their end-of-life care preferences and choices while they still have the cognition, capacity, and language to do so. Professionals often find this a difficult area to address. Studies show that there is inadequate preparation of both people with dementia and their carers for future care issues and related decisions, with some not engaging in ACP discussions at all (Cavalieri, 2002). Despite agreement on many aspects of end-of-life decision-making, physicians, nurses, and relatives hold different views arising from their religious beliefs, their assumptions about the perspectives of the patient, and their contrasting care responsibilities

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(Rurup et al., 2006). Where ACPs do exist, relatives often attach great importance to them and believe they *must* be followed, whereas with the widespread use of the Mental Capacity Act 2005, professionals know that only certain types of ACP documents have any legal standing (Rurup et al., 2006).

Advance care planning process and tools

ACP tools are emerging, with little evidence as yet for any improvement in associated outcomes for people with dementia (Denning et al., 2011). As part of a wider study in Australia, Caplan and colleagues (2006) used an ACP (Molloy et al., 2000) as part of a programme to reduce acute hospital interventions. The combination of education and ACP led to a reduction in emergency calls, fewer hospital admissions, and a decrease in mortality compared with homes in the control group.

In the UK, the Mental Capacity Act 2005 provides a legal framework for the ACP process. The Act gives competent adults in England and Wales the legal right to refuse treatment (i.e. artificial feeding and resuscitation) through the writing of an 'advance decision'. People can also make an 'advance statement' that reflects their general beliefs and personal values about the sort of care they would like to receive in the future.

Lasting Powers of Attorney (LPA) were also introduced through the UK Mental Capacity Act 2005 and enable the appointment of an attorney to make proxy decisions when the PWD no longer has the capacity to do so. A 'Personal Welfare' LPA allows the attorney to give or refuse consent to medical treatment, if such preferences have been expressed in the document.

Due to the advancing cognitive difficulties of the PWD, nurses and allied healthcare professionals must ensure they communicate with a main carer(s) in addition to the PWD in order that appropriate care and support is given. This can give rise to ethical and legal challenges, e.g. receipt of third-party information, disclosure of confidential health information, consideration of the PWD's capacity for decision-making, and potential disagreements among family members on the best interests of the PWD. This demands that dementia care professionals should be aware of the legal and ethical issues involved in ACP, as well as developing the skills required to embark on such difficult conversations.

Interventions in end-of-life care for older people

The role of nursing care and allied health professionals

Dementia affects the whole family, and people close to the PWD find themselves providing increasing amounts of care and support as the disease progresses. Hence, care delivered is required to be mindful of the whole family unit and the relationships therein. Various health and social care professionals have a role in supporting palliative and end-of-life care

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for PWDs. For example, occupational therapists may provide assessment of the home (or usual place of care) environment for equipment and adaptation needs; social care workers may provide assessment and provision of personal care and domestic support needs; district nurses may help in accessing vital equipment and meeting physical healthcare needs; physiotherapists may provide care and support, and advice on mobility and falls prevention, and chest care in cases of pneumonia. Many health and social care professionals are keen to provide better quality end-of-life care to people with dementia. In our own studies, using a rapid participatory appraisal methodology, we found that all professionals involved in palliative and end-of-life care in dementia were acutely aware of the limitations both in their own knowledge and skills and in the health and social care system within which they worked (Denning et al., 2012; Sampson et al., 2012). Many of the barriers to good-quality end-of-life care in dementia highlighted in this work were associated with lack of interagency communication, not having a clear dementia care pathway, and a sense of helplessness.

There are two very clear elements to good quality dementia care: the medical model/approach and the social model/approach. Both are inextricably linked and both of distinct value to the care delivered to PWD and their families. Early on in the illness it will be necessary to discuss the purpose of diagnostic investigations, what they entail, and how results will be given. This is an important time to establish a relationship with people with dementia and their family, understanding the main problems from their perspective, and liaising with other health and social care providers.

What is appropriate treatment at the end of life?

Despite the high mortality in advanced dementia, particularly for those who are admitted to the acute hospital, people with dementia receive as many painful investigations and procedures (e.g. arterial blood gas sampling) as, and are more likely to be physically restrained compared with, patients without dementia (Morrison and Siu, 2000a). This suggests that clinicians fail to adopt a palliative or supportive approach to patient care, possibly because people with advanced dementia are not perceived to be suffering from a 'terminal illness'. This may be due to poor understanding of the pathophysiology of dementia among healthcare professionals (Thuné-Boyle et al., 2010). Other vital components of good end-of-life and person-centred care are also neglected with little acknowledgement of spiritual needs, failure to withdraw inappropriate medications, and non-referral to hospital palliative care teams (Sampson et al., 2006). People dying with dementia in nursing homes often receive burdensome interventions. In an American study, Mitchell and colleagues (2009) found that 29% received enteral tube nutrition and 12.4% were hospitalized.

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The evidence base on palliative care in dementia is somewhat limited, particularly when compared to research on palliative care for people dying from cancer. Systematic reviews have identified how care mainly focuses on specific interventions such as fever management policies, pain control, or the withdrawal of care, i.e. *not* prescribing antibiotics, rather than a more active palliative model (Sampson et al., 2005; Goodman et al., 2009; Murphy et al., 2016). Good person-centred care requires a more rounded approach, and a number of multicomponent complex interventions and pathways have been developed that may improve the quality and outcomes of care for older people with dementia in the acute hospital and in the community.

Care management

There is a growing interest in a 'care management' approach for families affected by dementia; this entails detailed assessment of need and a coordination of care and support from health, social, and voluntary care professionals. Such an approach is considered essential in meeting the palliative and end-of-life care needs of people with dementia and their family carers (Judd et al., 2011). A care management approach is identified as a positive determinant of how well a carer is supported in his or her caring role (Hibberd, 2011), and is an approach that is best applied throughout the illness, from the diagnosis of dementia, living with dementia, to death and beyond in supporting families in their loss (Denning et al., 2017b).

Admiral Nursing is one approach in providing care management throughout the course of the illness (Denning et al., 2017b). Following diagnosis, appropriate follow-up is essential to discuss the prognosis and issues of legal and financial planning, give advice on the next steps, commence the discussion of ACP, and continue liaison with local services. Later in the illness, nursing and allied healthcare input will depend largely on symptoms and their management. Information and guidance provided within the context of continuing professional support, as in the case of Admiral Nursing (specialist dementia care nurses), is effective in supporting family carers and reducing anxiety levels (Wills and Woods, 1998). A distinct advantage of the Admiral Nurse service is the long-term nature of the work with families of people with dementia and the support offered throughout the trajectory of the illness; this support is of particular value during transitions from community to care home (Denning et al., 2017a).

Care pathways and policies

The English National Dementia Strategy (Banerjee and Owen, 2009) contained little regarding end-of-life care, and the English End of Life Care Strategy (Department of Health, 2008) made little specific reference to dementia. This illustrates how people with dementia fall through gaps in the health and social care system. The National Institute for Health and Care Excellence (NICE) guidelines for dementia (NICE, 2018) include

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some recommendations, notably about offering ACP soon after diagnosis and the application of other NICE guidance in relation to palliative and end-of-life care for adults (NICE, 2015).

End-of-life care pathways and decision-making tools

End-of-life care guidance for people with dementia is lacking and this has been made more problematic in England (and in some other countries) with the removal of one of the main end-of-life care guidelines that offered some structure: the Liverpool Care Pathway (LCP) (Ellershaw, 2007). The LCP was an approach to care for the dying, intended to ensure that uniformly good care was given to everyone thought to be dying within hours or within two or three days, whether they were in hospitals, nursing homes, or in their own homes. However, concerns were raised about how the pathway was implemented in practice, e.g. that food and fluids may be withdrawn too early from people with dementia (Treloar, 2008). After a highly politicized debate use of the LCP was phased out from the British health and social care system in 2014.

Davies and colleagues (2016) used an iterative co-design approach using qualitative interviews and focus groups with family carers and focus groups with health and care professionals to develop a toolkit of heuristics (rules of thumb) to support decision-making in practice. Four heuristic decision-making algorithms were developed; 1) eating/swallowing difficulties, 2) agitation/restlessness, 3) ending life-sustaining treatment, and 4) providing 'routine care' at the end of life. Each topic became a heuristic consisting of rules arranged into flowcharts. Such decision-making tools have the potential to be used alongside existing end-of-life care recommendations, adding more readily available practical assistance.

Complex interventions and care programmes: Interventions in hospital settings

Ahronheim and colleagues (2000) conducted a randomized controlled trial of an intervention in which people with dementia received assessment and care plan recommendations from a palliative care team with the goal of enhancing patient comfort in an acute hospital. The intervention did not decrease rates of readmission to hospital, average length of stay, or mortality, but there was a significant increase in written palliative care plans and patients received fewer intravenous drugs. The authors highlighted the 'unique barriers' to providing good end-of-life care, including prognostic uncertainty, and suggest that care planning may be more effective when done outside the busy acute hospital environment.

Lloyd-Williams and colleagues used multi-disciplinary prescribing guidelines on wards for older people with dementia. There was a significant decrease in the prescribing of antibiotics in the last two weeks

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of life and patients were much more likely to be prescribed analgesia, including opiates (Lloyd-Williams and Payne, 2002).

Interventions in nursing homes and specialist care units

Training and educational programmes on end-of-life care and ACP for nursing home staff appear to be effective in improving knowledge and increasing satisfaction with end-of-life care in bereaved family members (Arcand et al., 2009; Garden et al., 2016; Moore et al., 2017).

A specific approach in the US has been that of the Dementia Special Care Unit (DSCU). Volicer and colleagues (1994) compared this approach to nursing home settings and found that the DSCU, which provided a palliative care approach focusing on 'maintenance of patient's comfort rather than maximal survival', led to less discomfort, fewer antibiotic prescriptions, less use of intravenous drugs, and decreased transfers to the acute hospital. Mortality in the DSCU was higher but costs were significantly lower.

The UK Gold Standards Framework (GSF) is a multidimensional programme that supports and trains staff to identify residents requiring palliative or supportive care towards the end of life (<http://www.goldstandardsframework.org.uk/>). It uses a structured approach to recognize when the last year of life may have begun, to assess residents' needs, symptoms, and preferences, and to plan care around these, particularly in supporting people to live and die where they choose. Although not developed specifically for residents with dementia, the GSF developed for care homes attempts to enhance communication between GPs and other specialists, particularly out-of-hours care. Introduction of the GSF has been shown to increase the proportion of residents who have an ACP and to reduce the numbers admitted to acute hospitals (Badger et al., 2009).

Interventions in the community

The Palliative Excellence in Alzheimer Care Effort (PEACE) Programme is an American programme set up to improve end-of-life care for people with dementia. It takes a long-term disease management model, integrating 'palliative care into ongoing comprehensive primary care of persons with dementia over the disease course, from initial diagnosis to death' (Shega, 2003). The patient-centred principles of the programme include ACP, education on the disease process, improved care coordination, and family support. This is implemented by clinical nurse specialists who coordinate care between families, physicians, and other health and social care professionals. Those involved in the programme were more likely to die in hospice or a place of their choosing, less likely to die in the acute hospital, and their carers were more satisfied with the quality of care received.

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In the UK, the 'Hope for Home' service has supported people with severe dementia and their families, providing a multi-disciplinary and holistic model coordinated by a specialist in old age psychiatry. Preliminary results have shown that total cost savings of home care compared to nursing home care for 14 people was £696,930 and that 57% of participants died in their own home (Treloar et al., 2009)—a significantly higher proportion than would be expected in the UK general population (22%) (Gomes and Higginson, 2008).

Carers and relatives: Burden, grief, bereavement, and support

As the number of people with dementia increases, so also will the number of family carers, with current estimations in the UK of 670,000 (Lakey et al., 2012). Given that the period during which people with dementia require ongoing care is generally longer compared to other illnesses, this means that carers of people with dementia have a potentially long and tortuous journey ahead of them. Many carers are spouses and therefore likely to be old and to have physical or mental health needs of their own, to the extent that these may hamper their ability to provide care to the PWD (Denning, 2011).

However, the relationship that the carer had with the individual prior to his or her illness still remains and 'carer' is an additional but not a replacement identity for previous relationships and roles, e.g. husband or son. The changing nature of the relationship often requires physical and emotional adjustments throughout its course and it can bring a number of pre-death losses that cause caregivers to grieve (Liken and Collins, 1993). Liken and Collins stated that even when family carers are able to work through their pre-death grief, they cannot fully re-establish their lives until after the death of their relative.

It is often assumed that when a PWD is admitted into a long-term care environment this largely resolves the carer burden and stress. This is often not the case and may leave the carer with feelings of guilt at 'giving up'. They may feel they have gone against the expressed wishes of their loved one and they may have a sense of failure that they were unable to continue with care at home (Givens et al., 2011a,b). This can manifest itself in the carer at times being overly critical of the care provided, so it is important to consider that the previous levels of burden and separation stress (Kiely et al., 2008) may not be resolved and are in danger of going undetected and unsupported. Providing support to carers, recognizing the circumstances in which they find themselves, and allowing them the opportunity to talk about their situation can enable some to provide at-home care for longer periods prior to institutionalization (Etters et al., 2008).

Loss, grief, and bereavement

Caring for a PWD is considered more burdensome and 'unrelenting' when compared with other long-term conditions (Sachs et al., 2004), with

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increased vulnerability to complex or abnormal grief reactions (Schulz et al., 2008). Some carers find that they have grieved so much during the course of the illness that they have no strong feelings left when the person dies, yet others feel a further acute sense of loss when the person dies.

A sense of loss is one of the most powerful feelings that carers of PWD experience. This sense of loss and associated anticipatory grief can be felt while the PWD is still alive, and depending on the relationship with the PWD, the carer may experience grief for many forms of loss (see Box 27.2). How family carers experience and manage their grief reactions to the pre-death losses can influence not only caregiving outcomes but also subsequent adjustment once the PWD has died. It is therefore crucial that their grief is addressed (Almberg et al., 2000; Collins et al., 1993).

Box 27.2 Losses that may be experienced by a carer of a person with dementia

- The person they once knew.
- The relationship enjoyed prior to dementia.
- The future they may have planned together.
- The loss of companionship, support, or the special nature of the relationship.
- Loss of freedom to work or to pursue other activities.
- Loss of finances.
- Loss of lifestyle.
- Loss of childhood when a young person or carer.
- Bereaved female spouses are at higher risk of depression following death of their husbands/partners.
- Separation bereavement when the person with dementia is admitted into care.
- Regret and guilt.
- Loss or lack of social support networks.

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In a systematic review, Chan and colleagues (2013) described grief in dementia carers as a complex reaction to losses occurring before and after death, and argued that anticipatory grief is greatest in moderate-to-severe stage dementia and spouse carers, especially when the PWD is

institutionalized. Evidence about the prevalence of grief is less robust, with studies reporting anticipatory grief between 47% and 71% and complicated grief after death in around 20% of dementia carers. Carer depression increases with anticipatory grief. Being a spouse carer and being depressed are the strongest predictors of complicated grief after death (Chan et al., 2013).

It is important that bereaved carers of people with dementia receive follow-up care in recognition of their loss and bereavement. Many carers feel a second, and huge, sense of loss and they may also feel that their life no longer has the meaning that it has had for many years. Often the care services that were present in meeting the PWD's needs instantly withdraw, leaving a void in the carer's life. Carers are often discharged from services that were related to the PWD so their expressions of grief are often not observed or addressed adequately. Care, such as Admiral Nursing, that is delivered with a focus on the whole family affected by dementia will take into account carer issues and provide much needed support after the death of the PWD (Lloyd-Williams et al., 2017; Moore and Denning, 2017).

Conclusion

Older people dying with dementia often have complex physical and mental health needs. These require a multi-disciplinary approach that pays attention not just to physical symptoms but also to their spiritual and social needs, supporting their family carers and the staff that work with them, in a range of settings from community to the acute hospital. A number of promising care initiatives and pathways have been set up, most of which take such a holistic approach, in keeping with the core values of palliative care and the philosophy of those working in mental healthcare of older people. The recent research and policy interest in this field underlines its importance and provides hope that the care of many frail older people dying with dementia can be improved.

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The experience of dementia

Chapter: The experience of dementia

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Introduction: Tom Denning

The clinical and academic worlds have been relatively slow to tune into the voices of people living with dementia and those of their families and others who care for them. The assumption has been that it would be pointless to do so. However, this assumption has been shattered by numerous contributions. These have included books, blogs, films, and documentaries, as well as the emergence of organized groups, such as the European Working Group of People with Dementia.

The heroes of this movement are brave and articulate people who face many obstacles in being heard. One common problem is a grumbling scepticism about their diagnosis, along the lines of: 'If they can speak or write like this, then they can't have dementia.' This issue is met head on, for example, by Kate Swaffer (2016; 2017). There are, of course, many

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types of dementia, with different presentations, but it is clear from people's first-hand descriptions that they have subtle cognitive difficulties, for example, involving memory, word finding, visuospatial skills, and so forth. The push to diagnose dementia earlier means that the diagnosis may be given to people whose functional impairment is relatively mild and therefore not immediately visible. Importantly, not everyone with dementia is elderly. Therefore, accusing people of not having dementia seems offensive. We wouldn't do this to someone who says they have cancer or heart disease, would we? People who emerge as dementia activists are likely to be exceptional people, but this is not uncommon in other areas of life. For example, members of parliament often come from backgrounds that are far from representative of the constituencies that have elected them.

Diagnosis is clearly a turning point in people's lives—one that is often regarded with great dread as akin to a death sentence. However, it is clear that the reality is more subtle. From the clinical point of view, it would be helpful if giving a diagnosis of dementia led to tangible health benefits, such as increased survival or fewer hospital admissions. Objective evidence for this, though, is lacking (Dubois et al., 2016b; Pimouget et al., 2016; Aldus et al., 2020). Nonetheless, from the individual's point of view, obtaining a diagnosis is at least sometimes valued as an explanation of their experiences and an opportunity to access information and support.

This chapter aims to make a small contribution to these areas by following the course of dementia from diagnosis to the end of life, and beyond. Two parts of the chapter are written by people living with dementia (Keith Oliver and Hilary Doxford), about their experiences respectively of diagnosis and life afterwards. The third section (Louise Lafortune and Carol Brayne) considers the contribution of diagnosis and the evidence for and against identifying cases of dementia at the earliest possible stage. Now that it is possible to diagnose Alzheimer's disease prior to any symptoms, it makes it important for us to consider what the risks and benefits of this may be. The concluding account is provided by June Hennell, who cared for her late husband. In this chapter, we aim to present a balanced and authentic account of certain aspects of the journey through dementia.

Getting a diagnosis: Keith Oliver

The day began normally. The sun was shining. The BBC Breakfast weather girl predicted warm sunshine which pleased me as a trip in the sun is always better than in the rain. Dinner duty back at school awaited me, and it is *much* less hassle if the children are able to run around outside. Today, because it was so dry and warm, they would have the added bonus of playing on the field.

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My wife Rosemary and I arrived in good time. I hadn't been to this hospital before so I was more nervous about being late, and not finding the right reception area, rather than to receive the results of my MRI scan. Why would I need an MRI scan if I had problems with my balance and ears? I only briefly dwelt upon this question. I was relieved to be met by a friendly receptionist in a quiet, rather than crowded, foreboding waiting area. A promising start. What time is it? ... 10:15 ... my deputy would be standing in for me and conducting the assembly today. I did chat to her before leaving school last night and we agreed the story and the hymn—a story about being positive, and the hymn we chose was 'One More Step Around the World I Go'—that should go with a bounce as always, the children love that one.

Exactly on time the neurologist's nurse calls me in to have my weight and blood pressure checked. All very routine, I'm assured. Back into the waiting room. Break time back at school now—again, thank goodness for the sunshine.

Thoughts of school were interrupted by 'Mr Oliver, will you please come this way?' I was led, accompanied by Rosemary, across the waiting area to a typical doctor's consultation room. Square. Modern. Paperwork strewn across a table. Computer screen idling on the corner of a desk. NHS files much like the Department for Education equivalents in my office. And there, centre stage, was the neurologist, who, until this moment, was merely a name on an appointment letter. In the next few moments this was to change, but not only that: you could also say that my *life* was to change.

The consultant then asked us to take a seat and asked a series of questions about my health, why I had gone to my GP a month or so previously, to which I explained about the falls, the tiredness, the inability to concentrate, the petit mal type phases recently experienced. He listened intently to what seemed like a long explanation, but wasn't really. Then he embarked on a series of what I thought of as silly questions, what month is it, what season, who is the prime minister, count back from 70 in sevens—all very easy. Then onto him reading three words and asking me to repeat them—I hadn't a clue, where are we at this moment—can't remember the name of the hospital but it's in Margate, isn't that good enough? Then the three words/objects again—still they didn't register. This prompted him to pause and turn his attention (and ours, too) to his computer screen.

'Well, Mr Oliver, I think that the results of your scan and what you have said to me today is consistent with early stages of Alzheimer's disease.'

He went on to say that the GP had referred me for the scan to rule out a brain tumour. He assured me there was no tumour. Along with Alzheimer's, this was the first time this possibility had been mentioned.

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I was speechless. My wife was speechless. He sensed our shock, and went on to explain that this was at the moment only a suggested diagnosis and lots more tests and scans would be required in order for it to be confirmed. He then drew two helpful pictures, showing as he described it, a healthy 54-year-old brain; and then he drew mine based on the scan—he did try and explain the scan to us, but it was too difficult to draw sense from it. The comparisons illustrated by the drawings were helpful then, and subsequently, as we came to terms with the diagnosis and tried to explain it to our friends and family. By now I was regaining some sense of the moment. I began to realize that we'd need to have a serious dialogue. The first question revolved around the subsequent tests and scans. Then we moved to talk about carrying on working, which was what I wanted to do.

Next, we raised the question of our forthcoming, long-booked, annual trip to Australia. We were alarmed by his response to this which was ... not to go. Despite our remonstrating that 'everything is planned and paid for', his advice remained the same. Subsequently, I reflected upon this. I was determined, with Rosemary's support, to go ahead with the trip, albeit with a slightly amended itinerary, so I wrote to the neurologist to say I felt with us visiting friends and having been many times before the benefits far outweighed any potential risks. Thankfully, he was kind enough to send a written reply stating that if I felt well enough, then I should go. It left me though with the thought (which I've never forgotten) that had I taken his advice, as many people would have done in that situation, we would have missed a wonderful trip. And it has subsequently been followed by four more trips to South Australia, our beloved place in the sun.

The sun was still shining as we emerged from the confines of the hospital. I suggested to Rosemary, 'Let's have a walk on the beach nearby'—a favourite spot of ours, to clear our heads and take stock—and 'I'll ring school to get someone to cover my lunch duty.' That's what we did, and I turned to Rosemary the moment we felt the sand under our feet, and I said, 'One door closes and one door will open'. I didn't know which door it would be, but I was to be proved right.

Beforehand

I had been in teaching for 35 years and was the head of a primary school. I had all the skills and experience that you'd expect. I could meet deadlines, multi-task, and use a computer with a fair degree of expertise. I would keep my office door open so as to be accessible, and I could cope with the resulting distractions that would waft through into my office.

Health issues had been creeping up on me for some while, but in the last three months I had noticed more significant changes that I could no longer simply ignore. I had some unexpected falls. I felt wobbly, as if I was on a boat, all the time. I had fatigue and felt generally slightly unwell. I went to see my GP, who thought I might have an ear infection so he

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prescribed antibiotics. When these had no effect on my balance or health, he arranged an MRI scan and soon after that followed the appointment with the neurologist.

During the process of diagnosis

Having left the tender care of the neurologist, I landed up soon afterwards in Canterbury's Memory Clinic. My route through the continued assessment was complex because, despite my difficulties, the last thing I really wanted was a confirmed diagnosis. I tackled each assessment as being crucial and I tried to retain a positive attitude allied to a real determination to score as highly as possible. I quickly developed coping strategies to protect myself from my difficulties—something I still do. Over a period of three months, I had a number of cognitive assessments. I gave 100% effort to all of these and I would come away exhausted. I was extremely well supported and informed by the psychiatrist, the clinical psychologist, and her assistant. Every assessment was scored, analysed, and reported back to me at each stage. Gradually, a comprehensive picture emerged. In some areas I was functioning at best at about the 40th centile, but at worst was performing in the bottom fifth centile. This was really alarming, as especially with my background in education, I understood very well what this meant. Only nine months earlier, despite some worries at the back of my mind, I'd been well on course for an MA in educational leadership. By now, even following Coronation Street was a challenge.

At work, I was having some difficulties. I found I could not retain information so well. Not so much that I had problems with my memory—it was more that I found it hard to take things in or to bring information to my fingertips. I could only concentrate on one thing at a time. I began to have difficulties answering the phone. I confided my situation to my deputies and to the school secretary, as I thought they really needed to be aware. I managed to carry on to the end of the school year. The staff were beginning to be concerned that there might be a problem with my health. Over the summer, I reflected on my position, which was beginning to seem untenable. So, I returned in September for the first two days of term, and then took sick leave. When eventually I received a definite diagnosis, this brought my teaching career to an end on 1 April 2011.

Subsequently

People know how dementia is portrayed in the media, and by large sections of the public, and thus they are often frightened and can be depressed. Giving people encouragement to live in the moment and to take each day as it comes is essential. Coping strategies to recover and retain one's own personhood, skills, and enthusiasms are essential. Positive living requires the person living with dementia and those close to them to accept that not every day will be as clear as we would wish for.

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What we need are services that provide the opportunity for people to be interdependent, so that they can relate to others on a range of levels. Some people like the dementia cafe type model. Others prefer more active collaborations, such as the writing group we established through the Forget Me Nots, which is an active service user group in East Kent. Some people want to live life without reference to dementia; others want to fight it, others to live with it, and others alongside it.

Through person-centred care, I want to see a range of therapies and activities made available to people which are local, interesting, and accessible. Please keep people living with dementia on the radar—what is rejected now might be extremely helpful and appealing later. A care plan is central to the notion of Dementia Pathways. It must be written jointly with the person and a clinician and reviewed at a relevant period, perhaps every six months. A care plan worthy of the name should monitor the person's wellness in the light of the Pathways they are following, not solely their medication. The emphasis needs to be both realistic and positive. I remember being offered antidepressants on two occasions because the doctor—the neurologist—felt I would need them. However, I never cashed the prescription, and I know other people who have done the same. For some it might help, but medication shouldn't be regarded as the first solution.

Resources, such as post-diagnosis groups, are very inconsistent across the country. A range of disciplines such as clinical psychologists, psychiatrists, and occupational therapists need to be available. Some people are comfortable with the support of the GP, but others feel that the GP lacks knowledge and understanding of dementia. The worst feeling is that sense of being on one's own, with little or no effective support from outside the immediate family or social circle.

We must ensure that agencies work together and that the person with dementia is at the centre of this collaboration, not each vested interest or agenda. We need much better signposting and mutual support for professionals and the public. We *must* avoid the notion that the clinician's sole role is to diagnose and then hand over to the voluntary sector: some of the best post-diagnosis support that both I and others have received has been from clinical psychologists via these groups and through their support of the Forget Me Nots.

Often it is helpful to use metaphors to describe what it is like to live with dementia. One of the most accurate is that of the weather—the foggy days that are challenging and difficult, the cloudy ones when some things are clearer than others, and the sunny days we crave. In your reading of this account, I appreciate your consideration and consequently making it a sunny day for me.

After the Diagnosis: Hilary Doxford

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I was diagnosed with early onset Alzheimer's disease around December 2012. Since then, I have discovered I am one of the 25% of people given an Alzheimer's diagnosis that has the symptoms but does not have amyloid plaques in their brain. I have not been re-diagnosed or un-diagnosed. I am still in the early stages and some would probably say I have mild cognitive impairment (MCI), rather than the dementia diagnosis I have been given.

Five years on, my cognitive function is still above average but my short-(and now medium-) term memory is extremely poor. It was my failures on the memory tests and scans showing brain shrinkage that were the basis of my diagnosis.

I have been reading back over my notes and presentations made since I was diagnosed to help me decide how to present my thoughts and experiences. Initially I was thinking of having two sections, 'before 2017' and '2017'. But I have decided I can see four clear phases of my life since I was diagnosed:

1. Post diagnosis: The first five months
2. May 2013 to December 2016
3. January to September 2017
4. October to December 2017

I have decided on these as health wise, functionally, and emotionally, I can identify tangible changes within each period.

Post diagnosis: The first five months

Health

Unlike many people, I cannot recall the date I received the diagnosis, it was sometime in late 2012.

Although not wanting to hear it, I was relieved to receive the diagnosis as I finally had an explanation for my concerns of the last seven years. Now I could deal with something tangible and move on, instead of living a life of stress and worrying about the changes I was experiencing. I firmly believe that as an individual you can make a difference to the trajectory of a disease and, even if that is not true, you certainly can take control of what happens with your life whilst you still have your faculties.

My first question on receiving the diagnosis was, 'How long have I got before I will need support and care?' The answer was 18 months to two years. That bleak statement had a profound impact on my life over the next five months. Sleep became very interrupted. My brain would not switch off until the middle of the night as I tried to work out what to do with my remaining time and adjust to the impact I was going to have on my husband Peter's life.

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I was offered one of the standard drugs, which I took for a while but did not feel well, experiencing several side effects, the worst of which was falling over. The third fall was a particularly bad experience, when on a cold February day, we went to Weymouth to check our boat was OK. The ropes were slack so whilst Peter went on board, I started re-tying the ropes. I do not know how it happened, but one minute I was on the pontoon, the next I was in the freezing water, not knowing where I was or what was happening. I just knew that the rope in my hand was important and not to let it go. Fortunately, Peter and a friend managed to get me out. Peter decided that day we were selling the boat as I was unsafe. It is the biggest regret, as we loved that boat and loved being at sea: it was our escape from the stresses of life. That added to my guilt. I stopped that drug and tried an alternative. The first day I took the alternative, I thought I was dying: if breathing was not an automatic action, I would have stopped. I decided no more drugs; I would rather have a better quality of life even if it was for a shorter time.

My second question on being diagnosed was, 'What research can I get involved in?' The answer, fortunately, was 'I don't know'. I say fortunately, as being given no information I did my own research into research. Having worked as General Manager for the UK Renal Registry I knew a fair bit about clinical audit and research, and so I applied to become a research network volunteer for the Alzheimer's Society. The result of that has transformed my life, enabling me to 'live well with dementia' and I am convinced that this has helped to slow my decline. As I became more involved, I moved away from feeling desperate and fearful to a place where I experienced possibly the most contentment in my life so far.

Functioning

On being diagnosed, I am grateful that I did not hand in my notice at work as I am convinced that continuing to work has helped keep my brain active. I did tell my boss and immediate colleagues as they were having to deal with my oversights and memory lapses.

A close family member was ill at this time and so Peter and I decided not to tell anyone else about the diagnosis as we did not want to add to their worries. After all, nothing had really changed from yesterday other than I had probably lost some more brain cells and I now had a name for my troubles.

Emotions

On a practical level, it was 'business as usual', but I developed an overwhelming feeling of guilt at the burden I was going to be. Having been very independent (and selfish) I did not want to have to rely on anyone.

The other thing I was dwelling on far too much was the late middle/end stage of the disease. As I had only been married for four years, I was dreading the day I would not recognize Peter, would not understand that

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people were trying to help me, and would not be able to tell people when I was in pain. I decided I was never going to get to that stage and started looking into Dignitas. Once I understood what needed to be done, I did nothing more for the time being. I was angry at the UK's stance on assisted dying as it meant that I would have to go to Switzerland sooner than perhaps necessary to ensure I could get myself there independently. I did not discuss any of this with anyone, especially Peter, as I knew I would upset him very much.

May 2013 to December 2016

For the next three and a half years, I continued to work and the rest of my time was taken up with voluntary work and also participating in research studies and trials.

Health

I started to take high doses of vitamin B following a research paper I read. This had a noticeable (to me) effect on my brain function. Within a week or so, I felt as though my brain had improved to where it was two or three years earlier. Whether this was a placebo or actual effect did not matter to me: it made a tremendous difference, especially at work. My boss said I had stopped giving him blank stares when he was asking me about projects. And amongst other benefits, I was again able to remember the names of new staff members, as it had become embarrassing in meetings when I was unable to introduce them.

I had a 12-month follow up appointment after the diagnosis. I was excited as I believed I was managing quite well and that my decline was slow. I wanted this confirmed. I saw a different neurologist this time and he confirmed, as I hoped, that things were stable although he would not change the diagnosis.

Twelve months after that appointment I heard nothing. I was expecting another appointment so I called the memory clinic to be informed I had been passed back to my GP and they would not see me until I was re-referred. I was annoyed that I found out this way, but went to see my GP as I needed my driving licence to be renewed. I told him that I really wanted to know my rate of decline to give me some idea of what I should be planning for, and when. He said he would be happy to refer me again but, as I thought about it, I know the pressures the memory clinics are under and felt I was being selfish as the tests were not essential.

Functioning

During this period, it was easy to hide any difficulties I experienced. My IQ was still well above average and memory problems were addressed with better note taking and using reminders.

Over this period, I noticed that I had to focus more on completing a task in its entirety. I could not pick up a partially completed task without

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having to work through it again from the beginning. My typing accuracy was declining—I could not believe what I typed sometimes. Words would appear on the page that were not even in my conscious mind. Easily dealt with, it just needed more focus on proof reading. The downside though was that it took me up to 50% longer to do stuff. I did not want work to be aware of the difficulties so I would work longer hours to deal with it.

I would have meetings as required with my boss to discuss any changes we needed to make as a result of my declining abilities. He was very supportive and recognized that, after ten years of working for the organization, I had a 'knowledge capital' that was still of use. He said to me, 'You focus on what you can do and I will take care of the rest'. We did change my line management responsibilities. People who were not performing would sometimes exploit my memory issues to their advantage. Several times I was told I had said something I just knew I would not say, but I could not put my hand on my heart and tell them they were making it up. As a result, I felt much less confident. After this, we restructured and I now managed a small but incredibly supportive team who became Dementia Friends and understood my difficulties. Long sentences, complex paragraphs, and busy PowerPoint slides were hard to deal with, but I would break things down and get by.

Away from home, I do not like background noise. It distorts things and I find it hard to concentrate. However, conversely, I also find silence extremely stressful. I have to have the radio or TV on in the background at home and I seem to be able to shut it out and focus on the task in hand.

During this period, learning became a real problem. Stuff would go into my brain OK but I could not retrieve it when I needed it. If I was given a prompt or trigger, out it would come. Peter would frequently say, 'Can't you try a little harder to remember?', and I would respond with, 'I know whether or not I know the answer.' But I did start to wait a little longer before responding, and he was right, sometimes when I thought I did not know the answer it did, in fact, come.

I have learned a new memory trick. I noticed that if I imagined what I wanted to remember on a blank piece of paper then I do better at recalling it. I assume I am using my 'photographic' memory. I am not aware that I used this in the past. It still helps now; I even managed to recall a full address on a memory test. Maybe this is why I can still recognize people I have met only once, but have no idea of who they are, their name, or where I met them. I just know I have met them. There are always the funny incidents. I attended a two-day meeting and, going down for breakfast, I went and sat with a man I believed had been in the meeting the previous day. Taking out my notes I proceeded to enlighten him with my thoughts for 20 minutes or so. It gradually dawned on me he hadn't a clue what I was talking about, but he was very polite, making appropriate noises or nods as I rambled on. Eventually I said, 'You are not who I think you are,' which he confirmed, and I made a hurried exit.

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Another thing I noticed was that I used to recall my dreams vividly. Now I was either not dreaming at all or, if I had dreams, I could not recall them when I awoke. But, strangely, I discovered that if I got stung by nettles when walking the dog, more often than not, I would recall a dream the next morning. I started deliberately walking through nettles to see if it would help my recall, and it seems to do just that.

Satnav has been a saviour. I can no longer visualize a route I have been driving for eight years; instead, it appears as a jigsaw with missing pieces. When I was younger, I only had to drive a route once to know it for the future.

Emotions

At the end of 2013, Peter succumbed! Having heard dogs were good for people with dementia, he allowed me to have Tilly, who needed a home after a colleague moved abroad. He now loves her as much as I do and she makes such a difference when I feel low.

Peter is very sociable, and we would have visitors every weekend. I started to isolate myself and put a stop to having visitors and going out. This was primarily because I felt that I had nothing to talk about. I could not remember what happened yesterday, let alone last week. As a result, I started finding socializing very stressful, so I avoided it. One afternoon, driving home from work, I passed a massive barn fire with all the emergency services present and cows being herded to safety. 'Must tell Peter about this', I thought. When I got home 15 minutes later, it had gone from my mind, despite the usual 'anything exciting happen today?' question. However, it was so dramatic that it made the evening news, and then of course I remembered, 'Oh, I passed that on the way home'.

Another example of my shocking memory: we were fortunate to be invited to the Queen's 90th Thanksgiving Service, so I took a day's holiday to go but did not tell my colleagues where I was going. When I went into work the next day, they asked what I had been up to and I had forgotten I had attended the service. I could remember I had had a good day, but not why.

Over this period, I noticed I was becoming irritable and impatient, often with no valid reason. For example, I would get angry if a driver overtook me—how stupid; he was perfectly within his rights.

Decision-making was also harder, I would fret that I had made incorrect decisions. I would go over the facts as I could recall them time and again, trying to work out if I had missed anything essential. As a result, I started to avoid taking responsibility or making a decision.

I also started to eat more and gained three stone in weight.

During this period, I got involved in so many activities. These included media work, becoming a champion for Join Dementia Research (about which I am passionate), and also a member of the World Dementia

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Council and the Government's 2020 Dementia Programme Board. This involvement has forced me to keep my brain working. It has also given me so much hope but also frustration, in that I was seeing first-hand just how much was going on in the UK and around the world to improve the lives of those affected, but this was not being shared with those who really need to know. I saw examples of excellent practice and novel ideas that worked but many of these seemed to stop at a publication in a journal and presentation at a conference. In my view, policy makers, the research funders, and the researchers themselves place insufficient focus on dissemination and implementation.

Among other things, I also visited the dementia village at Weesp in the Netherlands. That visit convinced me that I could live with dementia even into the later stages, and so I now feel that I will not be travelling to Switzerland. Others need to see and know what is achievable. There is no working group of people with dementia in England, so I and some friends decided we needed to set up a group covering England, Wales, and Northern Ireland. That group is now known as the 3 Nations Dementia Working Group. At the time of writing, we are still a small group, but we have big ambitions to help and inform those affected by dementia.

January to September 2017

So, to 2017, where for the first time, I would say that my niggles are starting to become problems and issues. I have had to work much harder mentally to appear 'normal'.

Health

Another twelve months on and back to the GP for my driving licence review. I felt that there had been changes in my cognitive function this time and really wanted to do the tests again to see if my feelings were justified. This time I was told that unless I took treatment, the memory clinic would not see me. I laughed, as I wondered what treatment they could be talking about. It seems crazy to me, that I have to take drugs that I know will make me feel really ill in order to be referred. I just let it go, as again, despite changes, I can still manage and my GP was not concerned about my abilities. Also being involved in a clinical trial and other research studies, I was getting a lot of information on my condition, including the scan that showed that there was no amyloid deposited in my brain.

Functioning

I never appreciated that just thinking required an effort and could be so tiring. I have started to need to use quiet spaces to stop me wanting to scream out loud at times. In the past, I asked my brain for something and it would be delivered with no effort on my part. I now realize what a gift of a brain I had been given and regret I did not use it better. I was a member of Mensa, and it is only now I realize how hard some people must have been working to do what they did. As a manager, I know I was not

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the best and I wish I had had the insight back then that I now have. I must have made people miserable over the years by making unreasonable demands and by not appreciating that what was easy for me may not be so easy for others. I went from being a person who could instantaneously multiply two four-digit numbers to a person who cannot multiply a two-digit number by a single digit. It is demoralizing.

Things became increasingly difficult, to the extent that I decided I had to stop working in July 2017. I could still perform administrative tasks but more complex problem solving and dealing with management issues was too hard. In addition, my memory issues were getting worse, for example, I could no longer remember the names of colleagues who had recently joined.

I can no longer follow a plot or storyline in a book or on TV. However, I love documentaries and quiz shows, where I do not need to remember what's gone before. I may not remember anything afterwards, but it does not matter as I do not need to. This has advantages, as if I forget to watch something I wanted to see, I do not remember that I've forgotten!

For the last few years, I have been happy to travel alone in the UK, only wanting Peter with me when we go abroad. This is changing. I now find going to a new place quite stressful and occasionally frightening. I feel like I am adventuring into the unknown and do not like it. I am still doing it, but I feel that it will not be long before Peter will need to come with me to new places.

I like to do puzzles, both of words and numbers. This year, cryptic puzzles have become all but impossible. When driving to work, I used to work through the alphabet trying to name places beginning with each letter. A few years ago, I could manage 50 place names for most letters, this year, I am lucky if I can manage 10. So, I feel things are getting worse, although most of these difficulties are still easy to hide.

You had better not come to us for a meal more than two or three times, as my repertoire seems to now consist of three dishes. I cannot decide what to cook, and so I stick to the tried and tested of recent times. I have also noticed that I wear the same clothes over and over, my 'comfort' outfit. I cannot decide what suits me and what matches, so again I stick with the tried and tested.

Emotions

Emotionally, this year has seen changes. I do not know if it is the dementia or something else.

I thought stopping work would be really hard to deal with, but although I miss the structure it gave me, I have a great sense of relief and I had not appreciated how much I had been stressing over it. At least my voluntary work more than fills my days. However, one fear that I had about stopping

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work has come true. I feel my brain is slowing down and the cognitive difficulties are increasing.

Work worries have now moved to financial worries. Because of my relatively young age, I have a six-year gap with no income to manage before I am eligible for my pension. I am hoping to be able to work in an admin role or maybe in a care home.

I am really struggling to deal with examples of cruelty, both to people and animals. It upsets me greatly and ironically, I can remember it all too well. Animal charities sending literature with distressing photos play on my mind, and the TV adverts showing the appalling conditions people have to live with will not go away. It makes me feel helpless and hopeless. I cannot find a positive way of managing these emotions. I am finding it difficult and sad.

Words have always moved me and now I have to be careful with what I listen to when people are around, as again I have trouble controlling my emotions. I find it difficult to manage when things go wrong, even when they are out of my control. I have always been a bit of a control freak, but now I find it even harder to cope when things do not go according to plan. I rely more on Peter: in the past I would never pass a problem to him but now I find myself doing so more and more.

I really struggle to answer questions and make decisions that come out of the blue. I was at the fish counter and the assistant asked me whether I wanted it in a 'cook in' bag or a normal bag. I had decided what fish I wanted, job done I thought, so the follow up question totally threw me to the extent that I almost walked away in tears. Looking back, whichever answer I gave did not matter, but in the moment I could not rationalize.

I struggle to start up conversations on the spur of the moment. Previously, although I did not like socializing, I could start up a conversation when I was out walking the dog. If the other person has a dog I now rely on my 'stock' pieces: 'he's a lovely colour,' 'what a lovely face'. If they have not got a dog, I will not engage in conversation as I have nothing to say.

I have become very nostalgic. I have always had an interest and a love of history and archaeology, but this is different and new. I want to watch programmes and events from the 1940s to 1970s, despite being born in 1959. I find it comforting and easy.

I am now feeling that the world is moving on without me. I cannot keep up with all that is happening and I struggle to understand interactions, cause, and effect. In particular, technology is worrying me. I have always worked in or close to IT since the days of DOS programming in the late 1970s. Now, I do not 'get' social media. I cannot understand many Twitter messages and I do not have the time or desire to read unimportant (to me) trivia.

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However, then I worry that if I do not read them, I will miss something important. I worry that my bank account is going to be cleared out online or my identity stolen and so I do not feel in control anymore. I am starting to feel that I could take the easy way out and give up, handing everything over to Peter. But then I fear my decline will speed up.

October to December 2017

At the beginning of October having been out of work for two months, I felt I needed a 'reboot' and decided I was going to join some local groups, get fit, and lose the three stone in weight I had put on. I found a ballet and dance group for the over 50s and was about to sign up, when I slipped in our local woods whilst walking Tilly and broke my leg very badly (the second worst break that the surgeon had seen in his career). Ten weeks on and the bones have healed very well but I still cannot walk or even sit at a desk for very long.

It has been a reality check as to what it means to be disabled, albeit I hope temporarily.

I was in hospital for a week on a dementia ward. The staff were wonderful but stretched. The patients had no cognitive stimulation, no TV, radio, or other activity. I could see people declining over the week. The dementia-friendly clocks in the bays were great as they showed the day and date, but it was just a pity they showed the wrong day and date.

I had only one what I would call 'dementia moment'. I had been told the operation would take three to four hours. The anaesthetist came to see me and asked me if I wanted to have an epidural and remain conscious whilst they fixed my leg. I was not expecting the question and could not answer it. I felt he wanted me to have the epidural, whereas I had no desire to be awake. I got upset and was incapable of making the decision or assessing the pros and cons. Fortunately, the surgeon made the decision for me and I was knocked out.

When I came home, I found things noticeably harder. Possibly this was partly due to the pain, but I also felt that my cognitive function had declined. As we drove home, we were held up at a roundabout and I tried to count the cars in the queue ahead of us and could not do it. I kept thinking I was missing cars or counting them twice. Getting dressed, when putting on a strappy top, my arms would go through the wrong bit. Never a problem before. It is still early days, so maybe things will improve.

I am very frustrated at how long it takes me to do anything. The weird thing is every morning, when I wake up, I feel that I have only just injured myself. I have an overpowering feeling of déjà vu rather than a continuation of the recovery. I have never broken my leg before, but every morning I feel as though I am reliving a previous injury. When I think about it, I am frustrated that the fall has so far wasted three months of

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my life. But it does not feel like three months, my brain compresses anything dimensional into a 'moment', rather than real time.

All this has made me realize how hard it is to live with a disability and to stay positive. It is making me wonder how well I will cope if my decline continues. For now, it is easy to say I live well with dementia but I am becoming more aware of the difficulties that lie ahead.

Closing thoughts

I know how lucky I am.

I am constantly impressed by what people with dementia can achieve. I have a wonderful circle of friends and we support each other as we can comprehend each other's difficulties. Like everyone, we have good and bad days. Our bad days can be very depressing.

It was not until my brain stopped functioning as it once did that I appreciated the gift of a brain I had been given. Thinking was never tiring, but now I find it very draining.

There are those who question whether or not I have dementia. I have questioned it myself over the last few years. Then I stop and think about the difficulties I have now compared to before and how much harder it is to perform everyday activities. The changes are significant to me, although apparently not so to others. I know there is something wrong with my brain.

Two things in particular give me a wonderful life: my amazing husband and my adoring and adored little dog. They give me purpose and something to live for. I continue to live for today and count my blessings. I take time to enjoy the world and all that is good. Peter is my greatest blessing and my greatest worry. I know he will sacrifice his health and happiness to look after me and that worries me. He is a saint and my greatest sadness is what lies ahead for him.

Today, I do not need Peter as a carer, but I know if he were not always there quietly supporting me and loving me, things would be very different. I would be living in fear, but for now the fears I had are long gone.

The Serenity Prayer is now my mantra:

God, grant me the serenity to accept the things I cannot change

The courage to change the things I can, and

The wisdom to know the difference (*Reinhold Niebuhr*).

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Postscript

It is now April 2020, over two years since I last wrote. Quite a bit has changed for me.

My leg as predicted took nearly two years to repair, and 30 months on I am finally able to run again. I am still not working but need to find some form of employment. I have continued with voluntary work.

As for my dementia diagnosis, this is now being challenged by myself and others. Last summer, I was at a meeting at the Department of Health where a clinician I had not met before told me I did not have dementia. Initially, I thought, 'how can he say that based on hearing me speak during a meeting?' But then I considered that there are times when I wonder myself, and it is now eight years since I was diagnosed and I am managing just fine. This led me to ask my GP last August if I could be re-assessed. He was happy to refer me. I eventually saw a neurologist in January who requested a brain scan, which I had in February. Then coronavirus arrived in the UK and I am now waiting for the results. So, as I write, I am in a period of limbo, although I now doubt the dementia diagnosis, especially after reading a paper on Functional Cognitive Disorder (FCD) (McWhirter et al., 2020).

My symptoms and behaviours fit better with the description given of FCD, rather than dementia. My symptoms have not really progressed and in some areas, I feel I am improving or I have found ways to better manage them. I believe my cognitive abilities are stable. My memory problems persist, but there are glimpses of improvement in some areas. Sadly, we had to put Tilly to sleep 20 months ago. These days, my only really strong and detailed memories are of happy times with her and it still feels like only yesterday she was here. But then everything feels like it happened yesterday. I find I do well on remembering future activities such as meetings (ironically, missing meetings was one of my earliest problems). Strangely, once they have occurred, I have the same problem of retrieving and recalling them, even though I knew for weeks ahead what they were and when they were going to happen.

With the doubt over my diagnosis, for now I have stopped doing any voluntary work involving the general public but continue to support research and policy work where I feel I can justifiably do so. Some of my friends with a dementia diagnosis have also been told they do not have dementia because of how they speak in public. Several of them have found this very upsetting, as in clinical consultations, they are still being told they have dementia. The most upsetting aspect is the false hope it gives to their partners and family, which I can understand; if it turns out I do, after all, have dementia, I will be very upset for Peter.

The dementia diagnosis changed my life. If it was incorrect, so be it. I have been lucky in that my changed life, if a little more challenging, has still been good and given me many inspiring new friends and

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opportunities. It has had a significant financial impact, which I think at my age I will not be able to recover, which is a worry. But I understand how hard it is to accurately diagnose and I sought an explanation of my problems.

So today, I live in hope that I have FCD, that it will remain relatively stable, and that I will be able to find employment. I intend to put to good use what I have learned about dementia over the past eight years.

The contribution of an early or timely diagnosis: Louise Lafortune and Carol Brayne

To consider the importance of diagnosis we should start by listening to the voices of those who have direct lived experience of dementia, either through having a recent diagnosis themselves or by virtue of caring for someone with dementia. People living with dementia who have written and spoken about their experience have often drawn attention to delays in diagnosis and also advocated the benefits of early diagnosis. Although this sounds unobjectionable, it is worth thinking about some of the implications of this call to action.

It is likely that people writing about their own dementia may not be typical of the wider population with the condition. For example, they are likely to be better educated and to have had a younger onset of dementia than the majority. They may also have less-typical subtypes of dementia. On occasion, unfairly, doubt is even raised as to whether they really have dementia (for a discussion of this issue, see Swaffer, 2017). Therefore, while the accounts of dementia activists are extremely important and to be welcomed, we have to accommodate these alongside a bigger picture of hundreds of thousands of people with dementia who are less public in their views.

This section discusses some of the issues raised by diagnosing dementia, and considers the relative merits of screening, early diagnosis, and timely diagnosis.

The meaning of a diagnosis

There is a large literature on this area, most of which reflects that, until recently, dementia disorders have been diagnosed relatively late. Even cancer and heart disease tend to be diagnosed at the point of an event or through formalized screening. Under these circumstances, diagnoses are delivered by health systems and through particular investigations of reasonably well-established validity and prognostic value.

For conditions that are less straightforward, and involve clinical manifestations that are distributed in the population in a continuous manner, diagnosis is much more of a challenge. Conditions such as autism, dyslexia, and dementia fall under this area. However, the fact that dementia is subtyped into a series of ‘diseases’ suggests, wrongly, that

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the situation is more clear cut, and that the existence of the condition is a simple matter of yes or no.

In dementia we have the additional challenge that its frequency varies greatly with age. The dementia syndrome is very common indeed in extreme old age, with decline the norm towards the end of life in these ages. In contrast, dementia in middle and early late life is relatively rare. An individual with dementia at these ages is manifesting cognitive change at an age when this is unusual, rather than common, as it is in the ninth or tenth decade. Thus, the meaning and value of a diagnosis will vary according to age.

Diagnoses are made for many reasons—to establish the appropriately effective treatments, to provide prognoses, to label an individual so that that person or those around them can receive appropriate and available support, and as an explanation for changes that can be bewildering, distressing, and frightening without a label.

The tendency in modern dementia research is to push for biological definitions of disorders at earlier stages, even in the absence of clinical symptoms. In these circumstances, we need to think carefully about what we really want in relation to the diagnosis of dementia. Especially, we need to consider carefully, what is meant by, and what are the implications of the terms ‘screening’, ‘early diagnosis’, and ‘timely diagnosis’.

Individuals will need to consider what might be meant by an ‘early’ diagnosis, when there is little clear evidence of what the future implications of this may be. Societies should be concerned about the value of having substantial groups of people carrying labels of risk for dementia. This already occurs in the case of hypertension, where treatment is offered to asymptomatic people in order to reduce the risk of stroke and heart disease, but with the consequence that vast numbers of individuals are treated. Although the risks of major events are reduced for the population, the health care system incurs costs for all the treatment offered and the individuals are labelled as having a condition and placed at risk of side effects when they individually do not benefit.

The nature of dementia

‘Dementia’ describes a progressive clinical syndrome that encompasses difficulty in memory, language, and behaviour. When the resulting cognitive impairment is sufficiently great, such that there is interference with daily function, the patient is diagnosed with dementia of a particular type (e.g. Alzheimer’s disease (AD), vascular, frontotemporal, or Lewy body dementia). The incidence of most types of dementia increases with age, but each has its own natural history driven by a complex array of exposure to risk and protective factors throughout the life course. There is a growing consensus that the pathological process in the brain of

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people with dementia starts between ten and 20 years before the occurrence of the first dementia symptoms.

In turn, the clinical features that, when seen together, make up the diagnostic criteria are all continuous such that no fixed event defines the onset of dementia. Furthermore, one of the essential criteria for diagnosing dementia concerns impairment of day-to-day functioning, and this is variable across a range of social and cultural settings. There is thus no 'one test fits all' for dementia within life. It is possible to confirm a diagnosis such as Alzheimer's disease at post-mortem (McKhann, 2011; Beach, 2012), but even this is not straightforward since post-mortems are not often undertaken in routine practice. We also know from population studies that people over 80 years of age (that is, most of those with dementia) have a mixture of pathologies in their brains, and that these changes are also common in those who die without dementia (Brayne et al., 2009). To date, the diagnostic criteria for dementia remain controversial and are still changing (American Psychiatric Association, 2013). Although research criteria increasingly introduce biological criteria (e.g. Dubois et al., 2010), in routine practice the diagnosis still remains clinical and relies upon societal norms for cognition and function.

Greater understanding of the pathology and course of AD has led to it being reconceptualized as a disease continuum (Chen et al., 2016), though this idea is by no means new (Brayne and Calloway, 1988). There is a long phase with no symptoms, followed by a symptomatic phase of progressive cognitive decline, before the onset of functional impairment and overt dementia. As no treatments are available that significantly alter the natural history of the dementia syndrome, there has been an increased focus on dementia risk reduction and a shift towards diagnosing at an earlier stage, before patients have crossed the threshold into dementia (Dubois, 2016a; Jack et al., 2018).

The rationale for diagnosing at the earliest possible stage is that detection of people before cognitive symptoms start (i.e. at the prodromal or pre-symptomatic phase) or in the initial stages of cognitive impairment may lead to better outcomes, such as enabling better planning of appropriate current and future care and support, potentially delaying progression of cognitive decline, and improving general health outcomes for both patients and carers (Lin, 2013; Dhedhi et al., 2014).

Although these may appear perfectly reasonable arguments, this line of thought is controversial for dementia. The most important problem is that, for dementia, along with many other conditions, the more upstream (earlier) you go in the disease process, the weaker the evidence that detection by whatever means is actually beneficial for individuals or populations. So, the question for practice and policy—and society for that matter—is *where* in the disease pathway can we say that our understanding and the supporting evidence is good enough to ensure that we do more good than harm by shifting detection upstream?

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In the following sections of this account, we discuss what ‘early diagnosis’ actually means, present the current state of evidence for and against diagnosis ‘as early as possible’, and conclude with our view of where efforts should focus to optimize the journey through dementia.

Early versus timely diagnosis

Getting the diagnosis of dementia ‘right’ is high on health policy agendas for many countries. The last five to ten years has seen a steady cultural shift and proliferation of reports calling for ‘early’ diagnosis of dementia (Department of Health, 2012). These policies and the entry of the term ‘early’ diagnosis in public discourse has exposed a debate in the scientific and clinical press of what it actually means.

The prevailing view from many patients, their representatives, and professionals is that a diagnosis should be made as soon as possible in every individual case. This is understandably driven by personal and professional experiences of delays in access to diagnosis and appropriate support. Providing a *timely* diagnosis for an individual person, at an appropriate time, in their particular setting, is undeniably current good clinical practice, even if it is not universally available (Brayne, 2012).

‘Timely’ here implies an approach appropriate for the circumstances of individual patients, of benefit to the patient. It does not tie the diagnosis to any particular disease stage or chronological scale in the way that ‘early’ does (Brayne, 2012; Brunet et al., 2012; Nuffield, 2009). Yet the two terms are often used interchangeably, disregarding their different meanings, and with the emphasis often placed firmly on *early* diagnosis. This is unfortunate, since timeliness is not experienced in terms of simple chronological notions of time and, in the diagnosis of dementia, timeliness involves balancing a range of judgments (Dhedhi et al., 2014).

Until recently, before the current international emphasis on detecting dementia, recognizing and diagnosis of dementia relied on a ‘passive’ case-finding approach. Patients are evaluated for dementia because they or someone else bring a concern about memory, cognition, or behaviour to their GP, or because their GP raises the issue based on their clinical judgment (Mate et al., 2017). If this works well, the diagnosis would be made at the right time for the person with dementia at a stage where they, and/or those around them, will stand to benefit from it. Ideally, we would know from research at what point this is best for people at different stages of their lives, and with different risks of dementia.

However, more recently there have been moves towards much more active case detection—often driven by national policy. This has included estimations of the ‘expected’ number of people with dementia in localities, based on crude age distribution figures, without using the uncertainty limits that rigorous statistical analysis would require. At one stage, it appeared that dementia screening was being advocated, though the authorities have backed down from this in the light of reasoned

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criticism (e.g. Fox et al., 2013). The evidence for enhanced case detection and screening remains an area without robust evidence. No government or arm's-length agency has yet alleged that the evidence base is strong enough to recommend the costs and implications of nationwide screening programmes.

Evidence for and against diagnosing at the earliest possible stage

In the absence of any symptoms or concerns, early detection of dementia or detection at preclinical stages increasingly focuses on measures of biomarkers from body tissues (Dubois 2016a). This work aims to create large national or international groups of research-ready cohorts who have biomarker profiles indicating higher risk of progression to clinically diagnosed Alzheimer's disease within the individual's lifetime (e.g. the European Prevention of Alzheimer's Disease programme, or EPAD; see Ritchie et al., 2016).

Biomarkers (see Chapter 6 and Chapter 7) include peptides and proteins that are analysed in bodily fluids such as blood, urine, or cerebrospinal fluid (CSF), as well as brain imaging methods (Blennow and Zetterberg, 2018; Weiner et al., 2015). Biomarkers can be used in screening (prognostic markers; see Schaffer et al., 2015), as diagnostic tests for early disease detection (including detection of MCI; see Lewczuk et al., 2015), for predicting disease progression from MCI (Dickerson et al., 2013), and for treatment validation when used to monitor response to therapy (Blennow, 2010; Pillai and Cummings, 2013). The shift towards earlier diagnosis has occurred in parallel to the push for growing use of molecular biomarkers, not only as a diagnostic tool for dementia, but also for detection at the prodromal stage or in people with MCI. So far, not surprisingly, most of this work relates to Alzheimer's disease. Newer strategies include testing for profiles of genes, which together have been shown to confer increased risk (polygenic risk scores, e.g. Escott-Price et al., 2015) or a more individually tailored precision medicine approach using combinations of markers (Hampel et al., 2016).

However, we need to ask ourselves how well such tests perform and to what extent current evidence supports their use. The Cochrane Collaboration has developed a programme of systematic reviews of Diagnostic Test Accuracy for Alzheimer's disease to test the strength of evidence of various tests for early dementia. So far, these reviews have concluded that most tests have not been evaluated in sufficiently robust settings that relate to populations and clinical utility to be rolled out into routine practice. Despite this, the UK's most recent NICE guidance on dementia (NICE, 2018) recommends various forms of imaging and CSF testing to establish subtypes of dementia.

So far, rigorous research to test the hypothesis that treatment and management is altered by earlier or more intensive investigation for the benefit of the patient is lacking. It may help a clinician to feel more confident about their diagnosis, but the extent to which additional

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investigations actually benefit patients has not been demonstrated. Examination of a group of people seen in a true population study and assessed for a study diagnosis of dementia when compared with their medical records is one way of attempting to examine the value of a diagnosis, and what might influence the timing of that diagnosis. In the Cognitive Function and Ageing studies this was possible with an analysis of those people in a population-based sample who did *not* have a diagnosis in their medical records despite having cognitive impairment that could warrant a diagnosis as assessed by the study (Aldus et al., 2020). The mean time from first having discernible signs of dementia to obtaining a diagnosis was three years. People without a diagnosis tended to be older, to live alone, and to have predominantly non-memory symptoms. Importantly, though (in common with other studies), we found no demonstrable benefit of having a diagnosis in terms of any health outcomes.

The evidence base thus remains controversial for the use of tests for dementia within clinical settings. A further degree of uncertainty exists in the context of MCI, which itself is highly unstable as a diagnosis, especially in the group of worried individuals who present with subjective memory complaints. MCI is a state with a higher risk of subsequent dementia, but it is an inaccurate predictor, and probably the majority of people with MCI will not go on to develop dementia in the next few years. A significant proportion of people, especially those who are anxious about their memory, may indeed move back out of MCI into ‘normality’ over time (Matthews et al., 2008; Pandya et al., 2017).

Initiatives such as EPAD aim to research MCI and to offer medications at the ‘early’ stage of ‘disease’. However, especially among older people, a significant proportion with Alzheimer-type pathology will die before they ever would have developed dementia—if, indeed they would have ever done so. Honest communication with the participating public about the nature of the ‘risks’ of having MCI or evidence of biomarkers is therefore imperative. We will need to weigh the as-yet unknown risks of long-term brain-active medication (some substances could lead to brain changes that may be adverse), alongside the likelihood of the person developing dementia in their lifetime. Into this equation will come other variables, such as the person’s age, the possible role of risk and protective factors, and any evidence of neuropathology that they may have.

Future prospects

There is a real need to integrate the tensions described in this chapter. On the one hand, there are the very powerful voices of individuals—who may be very atypical in terms of their dementia, but who have important messages nevertheless—combined with pressure from biologically orientated researchers who wish to treat pre-symptomatic diseases. On the other hand, we have data from more ‘usual’ populations—these are

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people with the common forms of dementia, and often in the oldest age groups, with considerable comorbidity and thus much closer to death.

For this latter group, the area of early detection and screening may not be as valuable as some who advocate for these would think. Research is needed to test fully the different implications and implementations that might be necessary as the biomedical research efforts yield their results. The nature of the 'biomedical bubble' has recently been challenged (Jones and Wilsdon, 2018) and the Alzheimer's Society led roadmap (Pickett et al., 2018) provides a very clear mapping of the gaps that there are in the research needed for dementia as a whole in society—now and into the future. This will go well beyond the narrow disciplines currently dominant in the dementia research fields.

The end of the journey and life after dementia: June Hennell MBE

My husband, Brian, was diagnosed with frontotemporal dementia in 2008, about three years after the first symptoms developed. We wrote about our experiences living with his condition in the previous edition of this book (Hennell and Hennell, 2013). In late 2012, he was found to have prostate cancer and he died in July 2013. This chapter reflects on my experiences from this time and subsequently.

'You're the best thing'

Here's a snap-shot from December 2011. Stroking my neck, cradling me in one arm with a glass of Buck's Fizz in the other, 'You're the best thing that ever happened to me', said the man next to me in bed that morning. What inspired such an outburst? It was simply the effectiveness of the dementia medication.

A course of seven weeks of daily radical radiotherapy was due to start only six days from now. 'Where shall we go next New Year?' he said, immediately after we had been discussing this serious issue.

My usual reply, as a carer, would have been, 'Let's consult our "still to see list"'. However, this seemed like a facile thing to say when taken in context with us living with frontotemporal dementia and fighting an aggressive prostate cancer. Our struggles were greater because previously excellent dementia medication was being rendered much less effective by the hormone therapy that was being prescribed to block the testosterone that was feeding the tumour.

His next question was about our dog. 'How old is Jack?' 'Seven,' I replied. 'Gosh, I'll be eighty when he dies. I can't bear the thought of living without him.' Faced with such extreme optimism, I couldn't bear the thought of where this conversation was leading. If only it was possible for Brian to live until the age of eighty, I mused.

This caused me to reflect on how difficult it is living with comorbidity alongside dementia. Just imagine being told you have an aggressive

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cancer and then forgetting this vital information. When you are told that you are going to the hospital for a CT scan, you have to ask why. You then hear again the reason why but it doesn't remain in your library of chosen memories. When you go to the surgery for your hormone therapy injection, the nurse asks how you are. 'Absolutely fine,' you reply, because you are fine at that moment and you can't remember that a few hours ago you felt confused and distressed.

Life with two diagnoses

These issues are perhaps best illustrated by some extracts from my diary at the time.

'Did old Tommy die?' Brian asked, scratching his head. 'Yes,' I say, 'at least twenty years ago'. 'What did he die of?' 'He was ninety-seven,' I reply, 'so it was probably old age'. A puzzled look appeared upon his face and a settled contentment glowed in his eyes. 'That's good then because I thought that was another thing I'd forgotten ... not seeing him ... but if he is no longer around to see, I don't have a problem, do I?'

'Happy Christmas everyone,' said Brian when, on New Year's Eve, our family gathered to spend the evening together. Everyone felt that it could be our last such occasion. For Brian we were just starting Christmas, the festivities of the previous seven days completely unregistered.

Next day ... 'No, I won't wear my seat-belt and, if you insist on nagging me, I'll get out and walk. I don't care; I don't want to drive any more anyway'. The following day he got into the car, and fastened his belt before driving off. He had obviously forgotten the tirade and very draining experience for everyone else the day before.

'Did I feed Jack?' he asked, only five minutes after doing just that.

'I may as well move out now since I can't do anything right,' came the outburst after I had suggested Brian removed his muddy shoes before walking through the house. 'All you do is nag, nag, nag.' Where had all the good feelings gone?

Checking his dossette box (medication dispenser), I found that two days of important evening tablets had been missed. I realized that Brian can no longer remember to take them whereas he was almost infallible before starting hormone therapy. So, this is yet another thing that I am going to have to remind him about and he'll resent it ... and call it nagging.

'Oh! I'm absolutely fine, thank you,' was Brian's reply to the senior radiographer undertaking a radiotherapy review. Her raised eyebrow to me offered me the opportunity to comment. I was able

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to mention the increased deterioration in his dementia and the almost total absence of short-term memory.

Brian's inability to find our son's home five minutes away shocked me yesterday. Brian's inability to retain a telephone message long enough to write it down on the ever-ready notepad was a big disappointment.

These jottings are just from a couple of days of our living with comorbidity. I am left wondering how differently things may have turned out if cancer had not entered our lives.

Difficult choices

After 35 consecutive days of radical radiotherapy, we learned that hormone therapy will be needed for at least another two years to keep the tumour controlled. Our hearts sank for we knew the likely impact on Brian's behaviour of reducing the dose of his dementia medication.

We had to make choices and in April 2012 our decision was to stop the hormone therapy in favour of returning the Q to Brian's quality of life with dementia medication. We would let the cancer look after itself.

Brian's quality of life *did* return and throughout 2012 life went on. Our diaries were full of interesting social and dementia-related events, including the following examples:

- The Association for Dementia Studies at the University of Worcester had become very important in our lives. We were members of the LINK group, people with dementia and their carers who were happy to share their stories with students and to bring their experiences to influence course contents and research projects. Brian and I were invited to participate in many training events and we were filmed as part of the *Stand By Me* dementia training resource, which has now been converted to an excellent online tool. We gained a great deal of satisfaction from being involved. Feedback from the students and tutors was very kind, respectful, positive, and humbling.
- The Royal College of Nursing invited us to be part of the team designing *The Triangle of Care for Dementia* and it was with pride that we saw the finished material containing many of our contributions and a recommendation to read our booklets. I attended the government launch in January 2014 on my own.
- We were invited to contribute a chapter entitled 'Living Well with Dementia' for the *Oxford Textbook of Old Age Psychiatry*. Seeing the finished book and learning that it is translated into different languages and sold worldwide made us feel very humble.
- Healthcare authorities in Victoria, Australia asked permission to capture some of our ideas and reproduce them for their own use. We felt privileged.

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- We participated in staff training, research studies, conferences, and summits for The National Council for Palliative Care and NHS Gloucestershire.

Brian's walkabout

On 4 March 2013, I woke suddenly at 4 am to the barking of Jack, our black Labrador. At the front door, two Community Support Officers awaited me. I was informed that Brian was safe in an ambulance at the end of our drive. This was our first nightmare incident living with dementia. Brian had let himself out of the home, wearing no clothes or shoes and walked to the end of the drive and beyond, passing around sixty houses. By good fortune, he met a milkman on his morning round who was able to listen to Brian's questions, asking where he was, and subsequently called 999. Luckily, Brian was able to tell paramedics his name and mine, so we could be traced and reunited. However, Brian was sure that he was in Australia and had been watching the Ashes. He was quite simply lost and unable to identify his way home to the house in which he had lived for the last five years. Such is short-term memory loss, which prevents new memories being made. He was a serious risk of hypothermia on that cold March morning. How lucky we were.

Brian's comment later was simply: 'I don't know what happened but it is all right now, no harm done.' One learns to live with such understatements.

This incident made it necessary for us to change our routines and our home became like Fort Knox. I had to find ingenious excuses when Brian asked why the keys to the door had disappeared. But I had to keep him safe.

Changing times

As Easter 2013 approached, Brian's physical strength deteriorated, so we cancelled our planned break-away. We spent the time quietly at home. Brian's developing weakness meant that he could no longer take Jack for a walk and, as I couldn't leave Brian alone, I couldn't walk Jack either. Thus, with sadness and the help of our understanding daughter-in-law, Lorna, Jack was rehomed courtesy of the RSPCA, Stroud. All turned out well. Jack joined a lovely household and, many months later, when he asked where Jack was, I was able to tell Brian about what had happened. He was so grateful and, with hindsight, I give thanks for my timely action.

Brian's SAGE test

SAGE (Safer Driving with Age; <https://roadsafety-gloucestershire.org.uk/safer-journeys/driver/keep-learning/sage-safer-driving-with-age/>) is a programme run by our local Road Safety Team to provide support, guidance, and coaching to older drivers to enable them to continue driving for as long as it is safe to do so. It is not a test as such, but it

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probably feels like it! Early in May 2013 it had been arranged for Brian to take the SAGE assessment. By this time, he was starting to experience back pain and I felt that he was probably too weak to take this test. However, he wouldn't hear of cancellation, saying that he would simply take extra painkillers.

He was right! The examiner returned with a broad smile, pronouncing that the last hour had been a pleasure and that Brian was indeed safe behind the wheel. What a puzzle dementia is—and how many persons without dementia would be proud of passing such a test in their mid-seventies?

Hello Gloucester Royal Hospital

Brian enjoyed his 75th birthday on 8 June 2013, but just two weeks later he was taken to our hospital because of a severe internal bleed. He was admitted to an acute care ward, where the staff were very kind and accepting of me as Brian's carer.

We were able to contribute towards dementia care on the ward. For example, we took in a *This Is Me* booklet that we had completed for Brian. We knew that the staff read it because of the questions they asked. A blue butterfly motif was placed on the wall behind his bed to signify that he had a diagnosis of dementia. I was permitted to carry out Brian's personal care for as long as practical. Doctors consulted me at every turn. In fact, often I heard news before Brian did, and the medics clearly trusted me to tell him things at the right time.

One morning I was a little later arriving and Brian's bed was empty. The patient next door directed me to a bathroom and there I found Brian having a deep bubble bath, a lovely shave, and kind, caring attention from two healthcare assistants. It must have been a challenge for them getting him into the bath with the use of a hoist, but succeed they did and he felt wonderful afterwards. How kind they were and we told them so.

I was very grateful for the help for carers provided by the Patient Advice and Liaison Service (PALS), with free parking and reduced costs in the restaurant. I also appreciated being able to make myself hot drinks on the ward.

We enter the world of palliative care

When we learned with great sadness that Brian's cancer had spread into his spine, we were offered a visit from the hospital's Palliative Care Team. The nurse came specifically to see us the very next day. She was really knowledgeable and informative. She explained in detail what challenges might arise and helped me to make choices. I say 'me' because Brian was having difficulty staying awake, but she didn't stop the conversation simply because he opted out of it.

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Common sense prevailed and together we assessed that a hospice would enable Brian to spend his last days pain-free with 24-hour care. How grateful I was for this wonderful advice and for her professional and experienced approach. To most carers the subject of palliative care is new and, without help, can look like a minefield.

I had always suspected that preconceptions about end-of-life choices were pointless. Surely the all-round situation would need to be considered *at the time*, including the ability of the carer and/or family to cope? I now know this to be true. I am also aware that the availability of palliative care is quite variable from one place to another, making it into what we call a postcode lottery. This is unfair: everyone deserves the same quality of care at the end of life that we give to babies at the start of life.

And in palliative care, as in other parts of the dementia journey, it is very important for carers to receive informed support. Why doesn't it always happen?

Our hospice experience

I wish there were more hospices.

I felt wrapped in a comfort blanket; that feeling gave me confidence that everything would be dealt with appropriately whether I was there or not. Had I taken Brian home from hospital, I would have been too exhausted coping with his double incontinence to have quality time with him. Instead, we had three weeks of love, pain-free companionship, and expert care.

Nothing could have predicted it but, when staff recognized that there had been a change in his vital signs, I was called and came to return to Brian's side. I spent his last twelve hours with him. He died at 9.10 am on Monday 22 July 2013, having smiled and told me he loved me. I told him that I loved him too, dementia and all. Had he been at home, the changes in his vital signs could have gone unnoticed and he may have died alone.

Dementia Brain Bank research

We had both offered to donate our brains to the National Dementia Brain Bank in Bristol and their smooth system clicked into place following Brian's death. It was simple and unobtrusive during our time of grief. I was to receive results of their examination two months later, and I was pleased that this information may go some way to adding to the data bank for the future improvement of medication or prevention of this cruel condition. In due course my brain will be examined and used for comparative purposes.

My hopes for the future

My hope is that dementia will no longer be used as an excuse for denying people with the condition and their carers the right to make informed choices assisted by a palliative care team. I also wish that the horrors of

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comorbidity become better recognized. We all know that living well with dementia means making compromises, being flexible, and always looking for positive opportunities to increase quality of life.

However, when comorbidity becomes an issue, all such choices disappear. For the person with dementia, the arrival of a second condition can be devastating. It can lead to all sorts of new problems in managing either condition, or both. One example from our experience was that the dementia drugs became less effective when a second treatment was started. We have to encourage culture change among specialists working in silos, often in different clinics, hospitals, or NHS Trusts. The patient must be treated holistically across boundaries, with each clinician discussing the potential areas for conflict in their proposed treatments.

Going forward

I was grateful to many people for the help Brian and I had received, but I didn't realize how long my uphill struggle for survival would become following his death. I had lost *myself* in my caring role. When that role ended, not only had I lost the very meaning of existence, but I didn't know how to care for myself. These instincts had been buried beneath many layers of day-to-day coping.

It was on 15 August 2013, almost four weeks after Brian had died, that I hit rock bottom.

In retrospect, I realised that no-one should die during July or August. Trying to get support from recognised bereavement organisations simply didn't work. They were on holiday, or they had closed their offices in my area, or they didn't have email and only a phone connection on designated mornings. These times invariably clashed with my own commitments, such as having to attend another funeral, a hospital appointment, or whatever! I simply couldn't telephone them to 'register my needs'. I'd like bereavement services to take note: when a strong person seeks help, it is because they need it—and right now. Being told that there is a three-to-six month waiting list for bereavement counselling is particularly unhelpful.

So, I struggled on. It was only when the academic year recommenced and I was invited back to join colleagues at the Association for Dementia Studies at the University of Worcester that I cheered up. Attending my first events with them in September became a challenge, but I did it.

Friends and family said 'You know where we are. If we don't hear from you, we'll know that "no news is good news" '. In reality, it is very hard to pick up the phone and try to describe what you feel/need/want ... because you simply don't know. Nothing makes sense and the more you talk about it, the worse it becomes. Trying to make meaningful new daily rituals is very hard. I just wanted the phone to ring with someone saying, 'Hi, how are you? Fancy a coffee?', but it didn't happen often. People don't know what to say in bereavement, so they tend to say nothing, including

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avoiding one in the street. I had rarely thought about this before but I shall in the future.

Help came in many unexpected forms:

- Art lessons at Artlift, courtesy of a referral by my GP's surgery.
- Dancing on Prescription provided by the local district council, also by referral.
- Grand-children's hugs and sometimes innocent remarks about their 'Pops' all helped, especially five-year-old Ethan's commitment to looking for Pops' star in the night sky and Caitlin's pleasure at lighting a candle for Pops at every church and cathedral she visited.
- At the Positive Caring Course organized by the county council, I had met other carers with whom I bonded closely. We committed to meeting monthly at a local pub and our mutual support became a powerful influence for us all.

It is true that the first year is the worst, coping with anniversaries. But sitting through concerts where special memories came flooding back could also be heart-rending, not because of bad memories, but in learning to cope with good ones. For that was my problem: I couldn't recall bad times, only the privilege of a relationship, which I wanted back, that spanned 48 years.

My diary was full, but not overfull, with interesting invitations and gradually I resumed visits to London with organizations wanting to support me, but also to learn from my lived experience of dementia diagnosis to death or palliative and end-of-life care.

I was invited to join research boards, management committees, and advisory boards, and some of these I accepted. Ultimately, it was the grandchildren who saved my bacon and helped me to realize that their future was worth my survival. Now it is a thrill to take part in students' training sessions and conferences. They never seem to tire of hearing our story—'Better than textbooks,' they say.

On reflection

There are many things that I have learned from my experience as Brian's wife and as his carer. I reflect on these in the next few sections, and look at the direct legacy of Brian's life and his dementia, explore (explode?) some of the myths that exist around dementia, and finally offer some thoughts for dementia carers who have recently been bereaved.

Brian's legacy

The Hennell Award

It was a thrill for me in May 2014 to launch the Hennell Award for Innovation and Excellence in Dementia Care. Two of my eldest grandchildren, Katryna and James, came with me to the Association for

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Dementia Studies (ADS) at the University of Worcester for the launch and spoke inspiringly of their understanding of dementia and their respect for their Pops. I have committed to sponsor this award for five years. It is open to anyone registered with ADS who puts their learning into action in their workplace, creating innovation and excellence. Self-nomination is allowed but so is nomination by a manager or tutor. I want to reward motivated persons who, as Brian used to say, 'dare to be remarkable'. Full details are on the ADS University of Worcester website (see the end of the chapter for Internet link).

Stonehouse Memory Link

In October 2013, together with two local town councillors and a community builder, I launched Stonehouse Memory Link, which is a dementia awareness project for our locality. Our aim was twofold:

1. To learn from the experiences of those with memory loss how we could improve things for them in Stonehouse.
2. To provide a help line for those worried about their own memories or that of someone close.

We ran a poster campaign from which we learned that our town was fortunate in its provision of care. In October 2014 we launched a postcard campaign sponsored by the Barnwood Trust. By providing a postcard that people could complete and post to my address, we made help more accessible. We gained the support of GPs which was invaluable.

NASA

NASA reported that some astronauts had experienced depression and anxiety disorder while in low earth orbit. Scientists were looking at data from circadian and ultradian rhythms after processing with predicted algorithms. Clearly long-term activation of fight/flight responses can cause accelerated ageing of the brain. Data from spacecraft equipment can illustrate this using predictive algorithms and I am in close contact with a space expert who is interested in this research. Who knows how this may progress our understanding and help in the future dealing with dementia?

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In September 2014, I was privileged to help in the launch of a Foundation Degree in Dementia Studies for the Association for Dementia Studies. Working with the students in pursuit of excellence in their results continues to be thrilling and satisfying.

Dementia myths

During my time as a carer, a mentor for other carers, a guest lecturer in dementia, and an expert by experience, I have heard many myths spoken about dementia. Here are some of those myths and my reactions to them. These are personal opinions. Please remember, when you have met one

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person with dementia you have indeed met just *one* person with dementia. And when you have met one carer you have indeed met just *one* carer—for we are all unique in our acceptance, flexibility, positivity, and ability to make those compromises which are required to live well with dementia.

Myth 1: It is easy to get a diagnosis

You only have to *book an appointment with your GP and describe to them what you feel*. It is anything but easy for the person suffering symptoms of memory loss to explain realistically how frustrated and confused they feel. It is even worse for a family member who feels disloyal to be 'complaining' about the person's behaviour.

Akin to the situation with domestic violence, spouses may secretly fear that it may be their fault, that they have changed and caused the behaviour, or that they should be more understanding. Divorce versus diagnosis: ask yourself, how many relationships end because of personality changes and irascibility? Yet these can be symptoms of dementia.

Solutions to this include:

- *Write it down.* Writing brief notes of the date, time, what happened where, and what the outcome was, may help in many ways. It saves confusion with the GP. It ensures accuracy of recall without the emotional upset of being disloyal.
- As this will require some time, I recommend that you book a double appointment with the GP. Expect that they will need to arrange several tests to rule out other possible conditions. For instance, a urinary infection or vitamin B12 deficiency may be enough to create symptoms similar to dementia.

Myth 2: Getting a diagnosis of dementia is bad news

In fact, receiving a dementia diagnosis can be *good* news. It can be a relief that there is a cause other than marital problems for the unhappiness, frustration, and tension being felt. It can identify other conditions needing attention and open the door to obtaining medication and support.

Having a diagnosis can also help various practical issues, for example, that downsizing (property, plans, activities) may be a good idea. If the person is still driving, they should inform the Driver and Vehicle Licensing Agency (DVLA) of the situation. And it is a good time to think about establishing a Lasting Power of Attorney for Health and Finance while there is still sufficient mental capacity to keep the process simple.

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Myth 3: Diagnosis is a waste of time because there is no cure

It is true that there is no cure on the horizon, but there is help available which, if you remain in denial, you can't access. If you get a dementia diagnosis, you may be eligible for research trials, you may be prescribed medication, and you will certainly have access to information and organisations that can help.

If you get a diagnosis you may also gain in confidence, for there are many people living satisfactorily with dementia. Making compromises and adopting a 'can-do' attitude can mean that life, while never being the same again, need not lack meaning or the feel-good factor.

The financial implications of living in denial can mean job jeopardy, mortgage worries, and concerns about dependants and living accommodation. Getting things out in the open enables you to address each issue at the best time, involving benefits and advocacy if necessary.

Myth 4: Medication may work only for a while, so why bother?

This may not be true. All the time results of research, often provided by ordinary people reporting successes, are recommending different approaches. For instance, at first, memantine was licensed only for clinical trials. Now, in some circumstances, it can be beneficial to reduce reliance on some other drugs and add memantine too. Worldwide research is having success. We can also hope that there continues to be crossover in the effectiveness of drugs that were originally developed for other conditions.

Myth 5: People fear dementia and don't understand—it is best not to tell friends

In reality, the opposite can be true. Ordinary people can show understanding if they know how to react and how their actions can offer support. It really means honesty all round, enlisting help to make changes, and making compromises on social outings to play to the strengths of the person with dementia. For some people, there is the opportunity to be more informed for the future, in case dementia affects their own family. Of course, some people react better than others, so it is true that you *do* learn who your friends are, but this can be a blessing and not a hindrance. And there are opportunities to make new friends by activities such as attending memory cafes, carers classes, Singing for the Brain and other dementia-related events. Your dementia adviser or community nurse can signpost these for you.

If you have never been a person who joins in, dementia won't necessarily assist you to change your attitude to participation in the community. Loneliness, in that case, can be the ultimate outcome. However, sometimes people are inspired to seek help and making that first step towards sharing information may change your life.

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Myth 6: Health care staff don't understand

Often you may feel that you tell one person that you are a carer, but the message doesn't get passed on. They asked my husband things that he didn't understand but they didn't ask me. At times, nobody seemed to care.

I discovered that this really isn't true. There has been a lot of effort in recent years to raise levels of awareness and knowledge among health staff, across all professions and levels of seniority. For example, in 2013 more than 100,000 NHS staff received dementia training that emphasizes communication skills. Dementia education is a priority for Health Education England. There is a huge job to do up-skilling staff, but at least the commitment exists. A useful resource is the Royal College of Nursing's *Triangle of Care for Dementia*, published in 2014. This gives guidance, based on contributions from actual carers, of how healthcare professionals should work in partnership with carers and those with dementia.

Good communication is absolutely vital to any training for dementia care. Everyone needs to be taught the basics of memory loss. Someone with a poor short-term memory is quite vulnerable to emotions in the here and now. Sometimes, a recent bad experience can leave the person with a feeling of being down without knowing why. Information told to someone with dementia can be lost in seconds. Healthcare professionals sometimes overlook this, but they can often save themselves time and trouble by ensuring that they tell things to the patient and the carer together.

Professionals also receive training in the use of the Mental Capacity Act, which emphasizes that patients have rights and, as long as they have capacity, they should be consulted. To carers this sometimes makes little sense, but we have to accept that the Act is there to protect patients and encourage them to be involved in decision-making. Having a Lasting Power of Attorney for Health and Welfare can give you powers if the mental capacity of the person you care for diminishes.

So, many people *do* care and many staff *do* understand. I believe that healthcare professionals choose this career wanting to do their best for their patients. In my experience most of them succeed most of the time.

Myth 7: Hospitalization for someone with dementia is a nightmare

Hospitalization can be very difficult for the carer as well as the person with dementia, and generally we assume that disorientation is bound to occur. However, this is not always the case.

Various things can be done to reduce the risk of becoming confused. The blue butterfly scheme, where a blue butterfly sticker is placed at the head of the patient's bed, alerts staff that dementia exists. This permits a more considered approach to difficulties that could arise, opening the door to

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person-centred care. Staff shortages and time restraints can limit this, but intervention can be meaningful—I have witnessed it. Another useful thing is to take a completed *This Is Me* document and hand it to the nurse on admission. This will give the clinical team useful information about the issues that exist and provide possible solutions to them. It is essential.

I found that my husband slept like a baby in hospital, just like at home. When he was awake, he lived very much in the moment. If bored, because nothing was happening, he went back to sleep. If thirsty, he poured himself a drink and if he needed anything else, he tried to attract someone's attention. Because I spent all day there every day, he showed few signs of disorientation. He would not eat breakfast until I arrived, which became his way of coping and making a reality of this new existence.

We shouldn't expect the worst. It is *not* always a nightmare because there can be a level of adjustment that works. I communicated right from the start so that specialists and senior staff knew that I needed to be kept informed and involved in debates about anything important. I thanked junior staff when they performed routine personal care for my husband and they appreciated this.

New routines, travelling, and sheer tiredness can make things difficult for carers when the person for whom they care is hospitalized, but this can be partially offset by taking some time out and asking family or friends to take a turn. As carers, we find it difficult to stand back and look at the implications for ourselves of what we are doing, but we must try. We find it hard to ask for help at any time and, when we have left our loved one in the care of others, the isolation can be devastating. Conversely, we could turn hospitalization into the opportunity to place our confidence and trust in other people—and have a break ourselves.

Myth 8: Socializing is impossible with dementia

It is completely false that there is nowhere to go where people understand. Give people a chance to understand and be prepared to adapt yourself. There are numerous sources of meeting people, many of which are supported by the Alzheimer's Society, such as memory cafes, Singing for the Brain, and dementia advisers. Other places include local offices of the Carers Trust UK; local council events and other community functions; day centres; and community nurses and health centres. There are social interest companies, such as Dementia Adventure, who organize trips to appreciate nature in a supported environment. Organized short walks are held in many areas. Walk short distances before returning. Increasing regular short walks can bring all-round health benefits and improve the feel-good factor. Local parks can be a good place to meet others in an unchallenging environment. Cinemas may have special screenings for older people or especially for people with dementia. Even if they don't, you could choose to watch programmes with shorter films.

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Save money and thrill your family and friends by making your own personalized greetings cards. They will be valued and a good talking point if you add some extra memories of time spent together, courtesy of old photographs, magazine entries, tickets, and programmes. You could start a reminiscence series of coffee mornings with your friends and invite neighbours. You could identify similar interests to pursue. It is also worth mentioning the 'Keep Safe' scheme, where traders offer to make a phone call for anyone in distress who has signed up. There you know that showing your card in a shop with a Keep Safe logo on the door means that help is at hand.

There is so much help and support out there to make it easier for those with dementia and their carers to socialize.

Myth 9: Nobody listens—I am invisible

Reread the previous section about the options for social life! As well as this, many organizations are eager to learn from carers. Offer your input and it will most certainly widen your horizons. You can contact your local authority and take a carers class. There you will meet others in your situation; camaraderie, when things get tough, is *invaluable*.

If you are confident at writing, record your learning points for others. Write to magazines. Campaign for things to get better. Speak on local radio or to newspapers. You have a voice and you have influence if you want to use it. Buddy up with others if it helps.

Myth 10: The person I care for won't know me at the end of his life

You may fear that, in the last stages of dementia, the person you care for won't know who you are, and that dying will be a relief, the end of torment for your loved one, and a living loss for you. This is untrue.

Dementia itself causes *very few* deaths. Most people die of another condition, with dementia being quoted as a secondary condition. Where death occurs because of a major second condition, such as cancer, this can be before the dementia has taken away recognition of loved ones. As I have mentioned before, the arrival of a second condition can make dealing with the dementia much more complicated. It sometimes seems that the different specialists involved in the case don't talk to each other. Sometimes they don't work in the same hospital. At times, their treatments seem to work in different directions. This can be challenging. Often it is left to the carer to liaise between different clinics. It can be very helpful to get to know the medical secretaries so they can help sort things out.

Advance Care Plans can be really useful. Planning end-of-life care and detailing what really matters to both the person with dementia and the carer is very important, but only if it is reviewed regularly. When the end is near, it is important not to adhere rigidly to written expressions of

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choice, but instead to take into account various factors, including: the general situation; the cognitive ability of the patient; incontinence issues; pain management; blood sugar levels; and the ability of the main carer to cope. It must be remembered that a carer may already be near exhaustion and future sleepless nights and trying days may impact upon their *future* quality of life as well as the current.

As I have mentioned, palliative care teams can be worth their weight in gold. Staffed with experienced people who really understand the options, emotions, and confusion at such a time, they can steer a family through even the darkest hours. There is no substitute for open and honest two-way discussion, but reality must feature heavily in the decisions that are eventually made.

Chasing rainbows: Some words for bereaved carers

Living with dementia can be a challenge, but living without it can be worse. These challenges can bring deep closeness, and when the challenge has gone, there is suddenly an unmanageable gulf. You might think that some kind of preparation, almost like a bereavement apprenticeship, following diagnosis would help. However, the chasm of bereavement grief may surpass any attempts to prepare for it.

Therefore, to those carers still making a dementia journey I say, 'Try to value each day.' For when those days of being a carer cease, the horrors, like the pains of childbirth, quickly fade, leaving you at risk of unwelcome invasion by feelings of emptiness. That invasion by these pangs of loss defeats logic or planning, and it has nothing to do with guilt.

During the time of caring for a person with dementia, it may seem that life in the future without those challenges will be a great relief. Instead, afterwards, when they are gone, it seems to be that memories of the smiles, the hugs, the true joy in achievement living *with* dementia take precedence. The rainbow to wipe away the clouds of sadness will surely rise, creating a future of blue skies. It is that optimism that keeps us going.

Selected links

Artlife:

<http://www.artlift.org/>

The Butterfly Scheme:

<http://butterflyscheme.org.uk/>

Dementia Adventure:

<http://dementiaadventure.co.uk/>

The Hennell Award:

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<http://www.worcester.ac.uk/discover/the-hennell-award.html>

Keep Safe in Gloucestershire:

<http://keepsafeglos.org/>

Royal College of Nursing Triangle of Care:

<https://www.rcn.org.uk/clinical-topics/dementia/triangle-of-care>

SAGE (Safer Driving with Age):

<https://roadsafety-gloucestershire.org.uk/safer-journeys/driver/keep-learning/sage-safer-driving-with-age/>

Singing for the Brain:

<https://www.nhs.uk/Video/Pages/singing-for-the-brain.aspx>

Stonehouse Memory Link:

<https://www.gloucestershire-pcc.gov.uk/what-the-pcc-has-done-for-gloucestershire/local-projects-weve-supported/stonehouse-memory-link/>

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Mild cognitive impairment

Chapter: Mild cognitive impairment

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Introduction

Mild cognitive impairment (MCI) is a descriptive term that refers to the presence of cognitive impairment out of keeping with normal ageing but of insufficient severity to constitute dementia. The concept of MCI has evolved since its introduction, and at present it is considered to be heterogeneous both in terms of clinical presentation and aetiology. This chapter aims to outline the current thinking about MCI, including its underlying pathophysiology, diagnostic criteria, and a proposed clinician's approach to the diagnosis.

The concept of MCI

By logical extension, the definition of dementia in terms of cognitive impairment of sufficient severity to compromise activities of daily living and functional independence created the need to define a lesser state of cognitive impairment that did *not* result in such functional compromise.

Mild cognitive impairment

However, MCI was not operationalized as a diagnostic entity until 1999 when work on the Mayo Clinic Study of Ageing, a longitudinal community-based population study, highlighted a subset of participants with memory impairments of a severity that fell between that associated with normal ageing and dementia. This prompted the first diagnostic criteria for MCI (Table 29.1; Petersen et al., 1999) in terms of: i) a subjective report of memory decline; ii) objective evidence of memory impairment; iii) relatively preserved general cognition and function; and iv) the absence of dementia.

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Table 29.1 A comparison of MCI diagnostic criteria.

	Petersen, 1999	Winblad, 2004	IWG New Research Criteria for AD: Dubois, 2010, 2014			NIA-AA Criteria: Albert, 2011		DSM-5, 2013
Terminology	MCI	MCI (subtypes as defined in text)	MCI	aMCI	Prodromal AD	MCI: core clinical criteria	MCI due to AD	Mild neurocognit ive disorder
Self- or informant- reported <i>memory</i> complaint	x			x	x			
Objective <i>memory</i> impairment	x			x	x ³			
Self-or informant- reported <i>cognitive</i> complaint		x ¹	x			x ¹	x ¹	x ²
Objective <i>cognitive</i> impairment in		x ¹	x			x ¹	x ¹	x ²

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one or more domains								
Relatively preserved general cognition for age	x							
Largely preserved independence in functional abilities	x	x	x	x	x	x	x	x
Not demented	x	x	x	x	x	x	x	x
Additional requirements			AD biomarker negative	AD biomarker negative	AD biomarker positive: low CSF A β ₄₂ and high CSF tau/p-tau; amyloid PET	AD biomarkers uninformative /not tested	AD biomarker positive: see Table 29.2.	

¹ Listed cognitive domains that may be impaired include: memory; executive function; attention; language; and visuospatial skills.

² Listed cognitive domains which may be impaired under the DSM-5 criteria include: complex attention; executive function; learning and memory; language; perceptual motor; and social cognition.

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³ Objective impairment in *episodic* memory specifically is required for prodromal typical AD using the IWG criteria, characterized by a free recall deficit that does not normalize on cueing. This may or may not be associated with impairment in other cognitive domains. In the absence of episodic memory impairment, prodromal atypical AD may be diagnosed if the presentation fits specific clinical phenotypes that include cognitive impairment in other domains. NIA-AA, National Institute on Ageing- Alzheimer's Association; MCI, mild cognitive impairment; AD, Alzheimer's disease; aMCI, amnesic mild cognitive impairment; IWG, International Working Group; CSF, cerebrospinal fluid; PET, Positron emission tomography. Adapted from Petersen, R.C., Caracciolo, B., Brayne, C., et al. Mild cognitive impairment: a concept in evolution. *J Intern Med*, 275(3):214–28. Copyright (2014) John Wiley and Sons.

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The initial focus in the 1999 criteria on episodic memory as the core affected cognitive domain of MCI reflected the primacy of Alzheimer's disease (AD) as a cause of dementia and the occurrence of memory impairment as the hallmark presenting symptom of AD. Over time, in acknowledgement of the possibility that MCI could reflect problems beyond memory alone, the concept of MCI was broadened to include other cognitive domains such as executive function, visuospatial processing, and language (Table 29.1; Winblad et al., 2004; Petersen, 2004). In these revised 2004 criteria, cognitive impairment was classified based on whether a memory component existed (amnesic vs non-amnesic MCI) and whether impairment was seen across more than one cognitive domain (single vs multiple domain MCI). This 2x2 classification resulted in four subtypes of MCI, namely single domain amnesic MCI, multiple domain amnesic MCI, single domain non-amnesic MCI, and multiple domain non-amnesic MCI.

This expansion of the clinical extent of the MCI concept has occurred in step with an increasing appreciation of the heterogeneous nature of its underlying causes. Petersen and colleagues themselves posited that each subtype of MCI in the revised 2004 criteria had the theoretical potential to progress to a variety of dementias, with single domain amnesic MCI being most heavily implicated in progression to AD dementia (Petersen et al., 2001). Currently, the prevailing view is that the umbrella MCI term represents a transitional state between healthy ageing and dementia, with the latter caused by differing disorders. This biological diversity is evident in the use of biomarker-based tests to identify the underlying disease state in MCI patients, notably in the National Institute on Ageing-Alzheimer's Association (NIA-AA) workgroup guidelines (Table 29.1; Albert et al., 2011), which make specific reference to 'MCI due to AD' as the symptomatic, pre-dementia stage of AD. While the workgroup reiterates Petersen and colleagues' original emphasis that MCI is a clinically diagnosed syndrome, the NIA-AA extends the diagnostic process with guidelines for establishing AD as the primary underlying aetiology (Box 29.1 and Table 29.2).

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Table 29.2 NIA-AA research criteria for diagnosis of MCI due to AD, incorporating biomarkers.

Biomarker test outcome			=	Biomarker probability of AD aetiology	⇒	Diagnostic category
Aβ (amyloid PET or CSF)	+	Neuronal injury (tau, sMRI, or FDG-PET)				
Conflicting/indeterminant/untested		Conflicting/indeterminant/untested				MCI: core clinical criteria
Positive		Untested				MCI due to AD: intermediate likelihood
Untested		Positive				MCI due to AD: high likelihood
Positive		Positive				
Negative		Negative				MCI: unlikely due to AD

Aβ = beta-amyloid; PET = photon emission tomography; CSF = cerebrospinal fluid; FDG-PET = fluoro-deoxyglucose photon emission tomography

Adapted with permission from Albert, M.S., et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7(3): 270–9. Copyright © 2011 The Alzheimer's Association. Published by Elsevier B.V. All rights reserved. <https://doi.org/10.1016/j.jalz.2011.03.008>.

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Developed in parallel to the NIA-AA criteria, the Second International Work Group (IWG-2) criteria for AD (Dubois et al., 2010, updated in 2014) places less emphasis on MCI as a syndrome in itself, and more on AD as a distinct pathological entity characterized by a progression from a preclinical phase, prior to symptom onset, through to the occurrence of MCI and then on to AD dementia. According to this formulation, 'MCI due to AD' is considered to be 'prodromal AD', preceding the onset of dementia, and its diagnosis requires biomarker evidence of AD pathology in addition to the MCI syndrome.

In the absence of guidelines linking the clinical syndrome to distinct disease processes (notably AD), the clinical features associated with MCI are used also to define other syndromes that differ from MCI in nomenclature but are similar in terms of presentation. The *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5* (American Psychiatric Association, 2013) introduced a new classification of 'mild neurocognitive disorder' (mild NCD) that closely mirrors existing MCI criteria (Table 29.1: American Psychiatric Association, 2013). Paralleling the difference in severity of cognitive impairment that separates MCI from dementia, this new DSM-5 classification differentiates mild NCD from major NCD, with the latter diagnosis divided further in terms of underlying aetiology. Subjective cognitive decline (SCD) is another emerging concept (see Box 29.2).

Box 29.1 NIA-AA clinical characteristics supporting likelihood of MCI (diagnosed as per core clinical criteria) being due to AD

- 1 Memory impairment present
- 2 Progressive decline in cognition over months to years (very rapid decline may suggest prion disease, neoplasm, or metabolic disorders)
- 3 Lack of Parkinsonism and visual hallucinations (suggestive of Lewy body disease)
- 4 Lack of vascular risk factors and extensive cerebrovascular disease on brain imaging (suggestive of vascular cognitive impairment)
- 5 Lack of prominent behavioural or language disorders (suggestive of frontotemporal lobar degeneration)

Source data from Albert, M.S., DeKosky, S.T., Dickson, D. et al. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7, 270-9.

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Box 29.2 Subjective cognitive decline

As the concept of MCI has evolved, so too has the distinct phenomenon of subjective cognitive decline (SCD); namely, a self-perceived decline in cognitive performance in daily life, which does not reach the level of objective impairment required for MCI diagnosis (Jessen et al., 2014). The decline should be persistent and unrelated to an acute event. Cognitive testing is useful in helping to exclude an objective deficit that would suggest established MCI.

As with MCI, the possible underlying causes of SCD are many and varied. Longitudinal studies support SCD as a risk factor for MCI and AD (van Oijen et al., 2007; Reisberg et al., 2010). It is not currently possible to differentiate SCD in preclinical AD from SCD due to other causes, but the SCD initiative (SCD-I) working group, convened in 2012 to develop a conceptual framework and research criteria, identify features that increase the likelihood of preclinical AD, including: subjective decline in memory rather than other cognitive domains; onset within the last five years; age at onset over 60 years; worries associated with SCD; feeling of poorer performance than peers in age group (Jessen et al., 2014). Other potential aetiologies of SCD include non-AD neurodegenerative diseases, psychiatric conditions including depression and anxiety, attentional bias in normal aging, and medication- or substance-induced decline.

Comparison of studies investigating the rates of progression of SCD to dementia has thus far been limited by the heterogeneity of SCD definitions employed. Nevertheless, a systematic review revealed that 24% of individuals progressed from SCD to MCI over a mean follow up period of 4.1 years (11 studies) and 11% progressed from SCD to all-cause dementia over a mean follow up period of 4.8 years (28 studies) (Mendonca et al., 2015). The same review established that SCD individuals were twice as likely to develop dementia as healthy controls (pooled relative risk 2.07 over 28 studies with 3821 SCD individuals and 15009 controls): for comparison, in their meta-analysis, Mitchell and Shiri-Feshki (2009) found individuals with MCI have a relative risk of 13.8 for progression to dementia. The heterogeneity of SCD as a condition, the inherent instability of the diagnosis (with a tendency for some patients to revert to normal cognition, as in MCI), and the fact that the overwhelming majority of SCD individuals do not develop MCI and dementia, mandate that caution should be exercised when considering the prognosis of the individual with SCD.

Diagnostic criteria

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Epidemiology

The conceptual evolution of MCI has led to a number of challenges when considering its epidemiology. In particular, the fact that the definitions for MCI were developed in the context of a specialist cognitive clinic setting, with attendant detailed history taking and examination of patients, complicates its translation to large-scale epidemiological studies, where detailed clinical assessments are not routinely undertaken. This is reflected in the difficulties in estimating prevalence of MCI in the general population, as evidenced by the inability to perform a meta-analysis of ten studies of the prevalence of MCI as a result of between-study heterogeneity in choice and implementation of diagnostic criteria (Alexander et al., 2015). Studies have been forced to use a variety of adaptations of the MCI criteria to fit with already existing datasets. Those using the more recent diagnostic criteria, and with adequate sample sizes and clear methodology, have shown prevalence among older people to be between 5% and 20%, with incidence of 21–71 per 1000 people per year (Sachdev et al., 2015; Petersen et al., 2014; Roberts and Knopman, 2013; Ward et al., 2012). These figures bear comparison with those from the Mayo Clinic Study of Ageing, which prompted the introduction of the MCI concept. In this population-based study involving around 3000 participants aged 70–89 who were non-demented and cognitively normal or who had MCI at entry, the prevalence of MCI in the non-demented population was estimated at 15%, with amnesic MCI being twice as common as non-amnesic MCI (Roberts et al., 2008).

Many studies estimate much higher prevalence and incidence statistics than those reported in epidemiological studies using recent diagnostic criteria and uniform methodology (Brodaty et al., 2013; Wong et al., 2013; Ward et al., 2012). There are numerous factors that contribute to this between-study variance. Studies recruiting from community settings generally yield lower rates of prevalence and incidence than studies recruiting from specialist memory clinics; in the latter setting, the referral bias associated with the process of clinical referral results in a patient population enriched in terms of pathology by comparison with the non-referred general population. Retrospective studies are further limited by the fact that cognitive assessments employed at the time of data collection might not have been designed with detection of MCI in mind. Additionally, age-specific prevalence rates are not always quoted, and as the age ranges sampled vary between studies, it follows that prevalence will also vary. Finally, the use of qualitative, rather than quantitative, criteria to identify MCI leads to between-individual differences in the application of the diagnostic criteria between centres and researchers, and in the case of retrospective studies, cruder diagnostic algorithms may be employed where clinical judgment is more difficult to apply. Even when the diagnosis is based on some quantitative evaluation of the severity of cognitive impairment, the absence of a consensus guideline for cut-off scores in cognitive testing, or of the type of cognitive test(s) to be applied, results in the adoption of different cut-off scores (e.g. cognitive

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performance 1, 1.5, or 2 standard deviations below that of the control mean score), introducing further variability.

Prognosis

Four potential outcomes have been documented in prospective follow up of MCI patients: progression to AD, progression to non-AD dementia, stable disease without progression, and reversion to normal cognition over time (Matthews et al., 2008). The rate of progression from MCI to AD or other dementia varies across studies and is largely dependent upon source of referral. In memory clinics, clinical trials, and specialist centres, the rate of progression to AD dementia ranges from 10–15% per year, whereas for epidemiological studies in which participants are approached prospectively and followed up, the rates are lower at between 6–10% per year. Table 29.3 shows how a meta-analysis of 41 studies yielded differential rates of progression (Mitchell and Shiri Feshki, 2009). This difference in outcome mirrors the differential prevalence of MCI in specialist and population-based settings, and is likely to be due to similar factors, including the a priori probability of having an early dementia (which will be higher in specialist settings).

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Table 29.3 Progression of Mayo-defined MCI cases to dementia in a meta-analysis of 41 studies.

MCI disease progression	Cumulative progression (%)		Annual progression rate (%/year)	
	Specialist setting	Population-based setting	Specialist setting	Population-based setting
All-cause dementia	39	22	10	5
AD	34	29	8	7
Vascular dementia	6	5	2	2

Source data from Mitchell, A.J., Shiri-Feshki, M. (2009). Rate of progression of mild cognitive impairment to dementia—meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand*, 119(4):252–65.

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Mitchell and Shiri-Feski (2009) noted in their meta-analysis that the cumulative proportion of cases that progressed to all-cause dementia rarely exceeded 50%, even in medium-term studies with follow up exceeding five years, suggesting that in a significant proportion of MCI cases may not have underlying neurodegenerative disease.

Reversion to normal cognition is a well-documented alternative outcome in MCI studies. Population-based studies have consistently demonstrated that between 6% and 55% of those diagnosed with MCI appear to return to normal cognition a year later (Sachdev et al., 2013; Koepsell and Monsell, 2012; Ganguli et al., 2011). Single domain MCI classifications, particularly non-amnestic single domain MCI, appear to be the most susceptible to returning to normal cognition (Jak et al., 2009; Bickel et al., 2006). Other factors increasing the probability of reversion include: less severe objective cognitive impairment; lack of apolipoprotein $\epsilon 4$ allele; lack of informant corroboration of impairment; comorbid depression; and good blood pressure control (Sachdev et al., 2013; Koepsell and Monsell, 2012). The phenomenon of reversion is perhaps unsurprising, given the many temporally variable factors that may influence cognitive performance in older people, e.g. psychiatric comorbidity, physical illness, and medication usage. This is particularly relevant in community settings, where one deals with a more unselected population than that seen in a specialist memory clinic, and where the opportunity for extensive assessment and stringent application of MCI diagnostic criteria may be less forthcoming (Farias et al., 2009; Gauthier et al., 2006). However, there is evidence that in those who have previously had MCI and reverted to normal, the lifetime risk of subsequently developing MCI and dementia remains increased (Roberts et al., 2014).

The outcome of non-AD MCI has been less well investigated. Within the Canadian Study for Health and Ageing, Wentzel and colleagues (2001) followed those with presumed vascular cognitive impairment without dementia (vascular CIND) and found that of 149 participants, 46% developed dementia after five years. Patients with MCI after stroke are also at increased risk of subsequently developing dementia, with rates of 25% at two years reported (Altieri et al., 2004). However, improvements are also seen in some subjects (Ballard et al., 2003).

Ferman and colleagues (2013) studied 337 patients with MCI and found 49 progressed to probable dementia with Lewy bodies (DLB) over 2-12 years' follow-up, while 162 progressed to probable AD, 116 remained as stable MCI, and ten progressed to other dementias. For those with an initial diagnosis of non-amnestic MCI, the annual progression rate to DLB was 20%, compared with 1.6% to AD. Conversely, an initial diagnosis of amnestic MCI yielded an annual progression rate of 1.5% to DLB, compared with 17% to AD. The occurrence of REM sleep behaviour disorder (RBD) was found to be strong predictor of progression to DLB, with a history of probable RBD noted in 80% of DLB progressors. Similarly, Jung and colleagues (2017) followed 14 patients with MCI and

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RBD over three to nine years, with three patients progressing to DLB and a further two exhibiting DLB features.

The syndrome of MCI of frontotemporal type has been described in a small case series by de Mendonca and colleagues (2004), who found that a combination of clinical features (apathy, disinhibition, irritability), cognitive impairments (in attention, initiation, and conceptual thinking), and neuroimaging (frontal atrophy) was predictive of progression to a frontotemporal dementia (FTD) diagnosis within two years. The syndrome of mild behavioural impairment (MBI) has been shown to be a better predictor of progression to FTD (Box 29.3).

Box 29.3 Mild behavioural impairment

In recognition of the fact that some patients with dementia, particularly frontotemporal dementia (FTD), exhibit a prodrome of neuropsychiatric symptoms without cognitive impairment, Taragano and colleagues (2003) proposed criteria for a separate syndrome of mild behavioural impairment (MBI), consisting of: i) persistent behavioural changes and mild psychiatric symptoms, especially disinhibition; ii) no serious cognitive complaints; iii) normal activities of daily living; and iv) absence of dementia. They found that a diagnosis of MBI without cognitive symptoms predicted progression to FTD (in their 2009 study of 60 patients, 68% progressed to FTD, 3% to AD, and 2% to DLB), while a diagnosis of either MBI with cognitive symptoms or MCI with neuropsychiatric symptoms favoured progression to AD (of 59 cases of MBI with cognitive symptoms and 85 cases of MCI with neuropsychiatric symptoms, the rates of progression to AD/FTD/DLB were 42%/20%/4% and 43%/17%/2%, respectively) (Taragano et al., 2003). The International Society to Advance Alzheimer's Research and Treatment (ISTAART) have subsequently proposed revised MBI diagnostic criteria that allow for, but do not require, the presence of concurrent MCI (Ismail et al., 2016).

Causes

Causes of MCI include many underlying neurodegenerative pathologies, as well as potentially reversible metabolic, psychiatric, and drug-related causes (Table 29.4). Risk factors for the development of MCI include: advanced age; apolipoprotein $\epsilon 4$ allele; low level of education; vascular risk factors (smoking, type 2 diabetes mellitus, dyslipidaemia, obesity, and hypertension); cardiovascular disease (coronary artery disease, atrial fibrillation, congestive cardiac failure); cerebrovascular disease; depression; and anxiety (Roberts and Knopman, 2013).

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Table 29.4 Potential causes of MCI.	
Neurodegenerative causes	Other causes
• Alzheimer's disease • Parkinson's disease • Lewy body disease • Frontotemporal lobar degeneration • Huntington's disease	• Vascular cognitive impairment, including post-stroke cognitive impairment and small vessel disease • Metabolic (e.g. recurrent hypoglycaemia; hypothyroidism; liver or renal failure) • Nutritional (e.g. B12 deficiency; pellagra) • Alcohol-related • Drug-related (e.g. anticholinergics; opiates; benzodiazepines) • Psychiatric (e.g. depression; anxiety; schizophrenia) • Traumatic brain injury • Infective (e.g. HIV) • Inflammatory (e.g. multiple sclerosis; systemic lupus erythematosus; vasculitis) • Autoimmune (e.g. limbic encephalitis, paraneoplastic syndromes)

Neuropathology

As the clinical syndrome of MCI is likely to encompass a variety of different underlying aetiologies, the pathophysiology of MCI is generally approached using this same aetiological framework. As might be expected, AD pathology is most frequently observed in MCI, particularly amnesic MCI (Jicha et al., 2006; Petersen et al., 2006), with cerebrovascular disease as the next most frequent pathology (Markesbery, 2010; Bennet et al., 2005; O'Brien et al., 2003). Other molecular pathologies associated with neurodegenerative diseases, including synucleinopathy, are seen less frequently. In some cases of MCI, no observed pathology or non-specific pathology is identified (Saito and Murayama 2007).

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However, attempts to establish causal links between the presence of pathological change and the symptoms of MCI are complicated by two issues. First, there exists a high degree of overlap in the amount of histopathological change seen in the brains of cognitively normal older adults, MCI patients, and dementia patients. For example, the sequential spread of β -amyloid and tau neuropathology in AD is well described by the Braak staging system (Braak and Braak, 1991), but neuropathological changes predate the onset of dementia and are observed frequently in individuals without dementia. Both β -amyloid and tau pathology are observed in the brains of cognitively normal adults (Stephan et al., 2012; Braak et al., 2011). In MCI patients, the amyloid burden varies in amplitude and cortical distribution but largely appears to lie at an intermediate level between that seen in healthy ageing and AD (Markesbery et al., 2006; Petersen et al., 2006; Jicha et al., 2006). In contrast to β -amyloid pathology, the presence of which does not correlate strongly with symptomatology, there is a close association between tau pathology, neuronal loss, and cognitive impairment in MCI. Even in very mild AD, stereological studies have shown 60% loss of layer II entorhinal cortex neurons, indicating that there is already significant neurodegeneration by the time that individuals present with symptoms (Gomez-Isla et al., 1996).

The second issue is that multiple pathological processes frequently coexist in the brains of MCI patients. Jicha and colleagues' (2006) longitudinal community-based study of 34 MCI patients who progressed to dementia and underwent post-mortem analysis revealed primary AD pathology with concomitant cerebrovascular pathology in 35% of patients, and concomitant Lewy body pathology in 26% of patients. Furthermore, a non-AD primary pathological abnormality was observed in 29% of the participants who had progressed clinically to AD dementia. The presence of mixed AD and cerebrovascular pathology is especially common (Bennett et al., 2005), but determining the relative contribution of each to the development of MCI is challenging.

Biomarkers

Given the importance of identifying AD in its earliest stages, the use of biomarkers in the diagnosis of MCI has been extensively investigated. At present, these biomarkers can be divided into two categories, detectable either by neuroimaging (MRI or PET) or by cerebrospinal fluid (CSF) assays:

- Markers of amyloid deposition:
 - Reduced CSF levels of $A\beta_{42}$
 - Positive amyloid PET imaging
- Markers of downstream neuronal injury:
 - Elevated CSF levels of tau or phosphorylated-tau (p-tau)

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- Hippocampal/medial temporal lobe atrophy on structural MRI
- Hypometabolism in the temporo-parietal cortex on FDG-PET

In terms of the temporal progression of biomarker change in MCI and AD dementia, Jack, Sperling and colleagues (Jack et al., 2013; Sperling et al., 2011; Jack et al., 2010) proposed a widely referenced hypothetical model (Fig. 29.1), in which amyloid deposition is the first pathological change, occurring prior to cognitive impairment, followed by neurodegeneration and then symptom onset. According to this model, biomarker evidence of both amyloid deposition and neuronal injury is established by the time MCI is diagnosed.

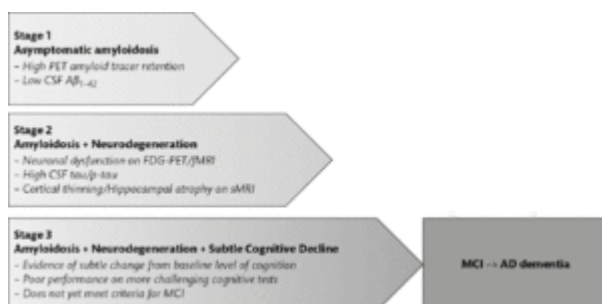


Fig. 29.1

Sperling and colleagues' proposed stages of pre-clinical AD. Some individuals may not progress beyond any one stage.

Reproduced with permission from Sperling, R.A., et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7(3): 280-92. Copyright © 2011 Published by Elsevier B.V. <https://doi.org/10.1016/j.jalz.2011.03.003>.

CSF biomarkers

In the context of clinically diagnosed MCI, CSF amyloid/tau biomarkers have been suggested to have prognostic value in indicating likelihood of progression of MCI to AD (Blennow et al, 2010; Hansson et al., 2006). A meta-analysis of 12 studies by Olsson and colleagues (2016) confirms significantly increased CSF tau and p-tau and significantly depleted CSF A β_{42} in MCI patients who progress to AD compared with patients with stable MCI. The sensitivity and specificity of CSF biomarkers for predicting progression of MCI to AD was further examined Ritchie and colleagues (2017) in a Cochrane systematic review of 15 studies encompassing 1172 MCI cases, of which 430 progressed to AD and 130 to non-AD dementia over the follow up period of up to four years. CSF tau sensitivities were quoted between 51-90%, with specificities of 48-88% (seven studies); CSF p-tau sensitivities were 40-100% and specificities

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were 22–86% (six studies); and the ratio of CSF p-tau/ A β ₄₂ yielded sensitivities of 80–96% and specificities of 33–95% (five studies). These rather cautionary results suggest that CSF biomarker testing in its current form is of greater value in identifying those with low risk of progression to AD than identifying those at high risk of progression. While this initially seems problematic considering the inclusion of biomarkers in the NIA-AA and IWG-2 research criteria above, there is potential for further work to be done to overcome existing limitations of CSF biomarker testing to improve accuracy and prognostic value (Box 29.4).

Box 29.4 Limitations of CSF biomarkers in MCI due to AD

Although CSF biomarkers are increasingly used in specialist clinics within the diagnostic workup of MCI, extensive validation work needs to be done before they are recommended for use in routine clinical practice. At present, there remains a paucity of research comparing individual biomarkers or combinations of biomarkers with one another in multivariate studies and there have been few studies directly comparing biomarkers in life with post-mortem data. It is therefore currently difficult to understand the relative importance of different biomarkers when used together or to interpret results when biomarker data conflict with one another, e.g. when CSF amyloid is low but CSF p-tau is normal. Furthermore, normative values for each CSF marker vary according to age: CSF tau and p-tau both increase with age over the lifespan of cognitively normal adults, while the association between CSF A β ₄₂ is complex, modified by both gender and APO ϵ 4 status (Li et al., 2017). Finally, interlaboratory variations in CSF biomarker results can arise as a consequence of various factors (including differences in CSF acquisition/storage protocols and assay kits). As the field of CSF biomarker research matures, harmonization of standardized operating protocols and implementation of an international quality control programme will address many of the current limitations.

Neuroimaging changes in MCI due to AD

Amyloid PET

Amyloid PET imaging, using either ¹¹C or ¹⁸F ligands, is listed by both IWG-2 and NIA-AA research guidelines as a means for determining the presence of underlying AD in patients with MCI due to AD. Comparison studies of CSF and PET biomarkers have shown a very high concordance between low CSF amyloid and abnormal amyloid PET deposition (Palmqvist et al., 2015). While the ¹¹C-based Pittsburgh Compound B was the first amyloid PET ligand to be introduced, the short half-life of ¹¹C has

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seen its usage overtaken by longer half-life ^{18}F ligands. In terms of the sensitivity and specificity for AD, a Cochrane systematic review of nine studies encompassing 274 MCI patients indicated that amyloid PET was sensitive, but not particularly specific, for MCI due to AD (S. Zhang et al., 2014). In this review, 112 out of 274 MCI patients (34%) converted from MCI to dementia during follow-up, with positive amyloid-PET yielding sensitivities ranging from 83–100% and specificities of 46–88% for predicting conversion. As with other markers of amyloid deposition, amyloid PET positivity is seen in cognitively normal adults and increases with age, accounting for its low specificity: one prospective cohort study of 177 healthy controls observed positivity in 18% of 60–69 year olds, 37% in 70–79 year olds, and 65% in those aged over 80 years (Rowe et al., 2010).

Tau PET

Historically, in vivo imaging of tau has been more challenging than amyloid imaging because of its intracellular aggregation. The development of tau-specific PET tracers, e.g. THK5117, THK5351, AV-1451, and PBB3, has changed this. Early studies of tau PET imaging show tau deposition in the medial temporal lobes of MCI patients, consistent with Braak staging of neurofibrillary tangles, and extension of tau PET changes into the neocortex correlates with progression of cognitive impairment (Cho et al., 2016; Johnson et al., 2016). As such there is considerable interest in the future use of tau PET as a biomarker for use in future clinical trials as an outcome measure.

Structural imaging: CT

CT scanning is used primarily to exclude alternative cerebral pathologies when MCI due to AD is suspected, such as malignancy, bleeds, and normal pressure hydrocephalus. While global and regional brain atrophy are detectable on CT, volume loss is more easily detected on MRI in view of its higher spatial resolution (O'Brien, 2007).

Structural imaging: MRI

Whole brain atrophy and atrophy of medial temporal lobe structures, such as the hippocampus and entorhinal cortex, are commonly seen in MCI due to AD (Frisoni et al., 2010) and can be predictive of progression from MCI to dementia, with 73% sensitivity and 81% specificity reported in one meta-analysis (Yuan et al., 2009). The importance of MRI evidence of neurodegeneration is reflected in its inclusion as a diagnostic marker in both the IWG-2 and the NIA-AA guidelines. However, two cautionary observations need to be considered. First, atrophy may not be detected in the earliest stages of any neurodegenerative disease and may therefore not be present in earlier stages of MCI. Second, hippocampal atrophy is not specific to AD, and can occur in normal aging as well as in non-AD disorders such as syndromic variants of frontotemporal dementia (Chan et al. 2001, van de Pol et al., 2006), though less so in Lewy body dementia

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and subcortical vascular dementia (Burton et al., 2009). Improvements in the diagnostic specificity of hippocampal atrophy for prodromal AD may be achieved with longitudinal studies of atrophy rates (Leung et al., 2013), combinations of different structural MRI measurements (Falahati et al., 2017; Eskildsen et al., 2013) or use of high-resolution MRI to measure hippocampal subfields (Khan et al., 2015).

FDG-PET and SPECT

Single photon emission computed tomography (SPECT) and fluorodeoxyglucose photon emission tomography (FDG-PET) studies in MCI patients respectively show hypoperfusion and hypometabolism affecting medial parietal areas (including the precuneus, posterior cingulate, and retrosplenial areas), consistent with their early neuropathological involvement in AD (Chetelat et al. 2005; Pakrasi and O'Brien, 2005). In terms of predictive ability, a Cochrane meta-analysis found FDG-PET to be 76% sensitive with a median specificity of 82% for predicting progression from MCI to dementia (Smailagic et al., 2015), while a separate meta-analysis found SPECT to be 84% sensitive and 70% specific (Yuan et al., 2009).

As a hypothesized marker of downstream neuronal damage in the temporal model of AD (Jack et al., 2013), hypometabolism on FDG-PET appears to have good specificity for differentiating AD from other neurodegenerative diagnoses. Silverman and colleagues (2001) conducted a longitudinal study of MCI patients with FDG-PET scans. Among the 138 patients who developed dementia with confirmed neuropathological diagnosis, FDG-PET correctly predicted the presence or absence of AD in 88% of cases, with 94% sensitivity and 73% specificity. In a study of 548 individuals (consisting of 110 healthy controls and 114 MCI, 199 AD, 98 FTD, and 27 DLB patients), Mosconi and colleagues (2008) found disease-specific FDG-PET patterns allowed correct identification of 95% of AD, 92% of DLB, and 94% of FTD patients. The study also identified differential patterns of hypometabolism within the MCI group, with an AD-like PET pattern seen in 79% of MCI patients.

Additional imaging modalities

Structural imaging (CT or MRI), amyloid PET, SPECT, and FDG-PET are all used to varying degrees in the diagnostic workup of MCI with usage dependent on several factors including clinician preference, cost, and availability of scan options. In addition to the aforementioned imaging options, there exists a number of additional imaging modalities that are being extensively investigated in research studies of MCI, most notably the US-led Alzheimer's Disease Neuroimaging Initiative (ADNI, <http://adni.loni.usc.edu>), but currently lack validation as potential clinical diagnostic tools. Some of the more extensively studied modalities are summarized in brief next.

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MR Spectroscopy

Magnetic resonance spectroscopy allows non-invasive, in vivo measurement of the concentration of different brain metabolites that may be affected by neurodegenerative processes. Several spectroscopic alterations have been described in MCI, including changes in the myoinositol/creatinine ratio (Kantarci, 2013) and reduced N-acetylaspartate (NAA) within the hippocampus (Ackl et al., 2005). Given that myoinositol and NAA respectively reflect glial activity and neuronal integrity, these MRS data may provide some mechanistic insights into alterations of brain function in early AD. γ -aminobutyric acid (GABA), glutamate, and glutamine are also significantly reduced in amnesic MCI patients when compared with age-matched controls. However, this reduction does not correlate with amyloid PET positivity, suggesting that these metabolic changes are unrelated to amyloid deposition and perhaps reflect other aspects of AD pathophysiology (Riese et al., 2015).

Functional MRI

Functional MRI (fMRI) involves the detection of changes in blood oxygen level-dependent (BOLD) signal that reflect regional or network activity within the brain. Imaging may take place while an individual is in the resting state (rs-fMRI, also known as task-free fMRI) or while performing an explicit task (task-related fMRI). Changes in functional connectivity in MCI and early AD have been detected using rs-fMRI, particularly within the default mode network (DMN), a network most active under resting conditions and involving many areas including regions within the medial prefrontal cortex, medial parietal cortex and medial temporal lobe (Yeo et al., 2011; Greicius et al., 2003). Sorg and colleagues (2007) observed significantly reduced DMN activity in amnesic MCI patients, particularly in the posterior cingulate cortex and hippocampus, which they hypothesized was an early marker of the specific functional connectivity changes observed in the DMN in AD. As rs-fMRI techniques have developed, widespread disruption of functional connectivity has been noted in amnesic MCI patients, both in areas of the DMN known to be associated with early amyloid deposition and in areas in which AD pathology is observed at a late stage of the disease (Minati et al., 2014).

Initial task-related fMRI studies involving episodic memory paradigms were previously suggested to demonstrate hyperactivation of the medial temporal lobe in MCI patients and hypoactivation in AD patients. However, a subsequent meta-analysis of 75 studies concluded that differential hypoactivation is detectable on task-based fMRI in MCI and AD, but that patterns of hyperactivation appeared similar in both, suggesting a possible compensatory mechanism to pathological connectivity changes in both MCI and AD (Li et al., 2015).

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Diffusion tensor imaging

Diffusion tensor imaging (DTI) uses the diffusion patterns of water molecules to map white matter tracts in the brain, and is interpreted often in terms of fractional anisotropy (the extent of directional restriction of diffusion) and mean diffusivity (the magnitude of diffusion). White matter tract damage and neuronal loss are thought to be reflected in decreased fractional anisotropy and increased mean diffusivity, both reflecting the increased movement of water within the tissues as barriers to diffusion are disrupted (B. Zhang et al., 2014). Such changes have been observed in the hippocampus and fornix to varying degrees in MCI and AD patients (Zhuang et al., 2013; Clerx et al., 2012; Zhuang et al., 2012).

Neuroimaging changes in MCI due to non-AD disorders

Vascular cognitive impairment

MRI changes suggestive of a vascular component to MCI include white matter hyperintensities, infarcts and haemorrhages (Hachinski et al., 2006). While the relative contribution of such MRI changes to a patient's MCI symptoms is poorly quantified, the presence of white matter lesions on MRI in older people, especially when of greater severity than appropriate for age, carries an adverse prognosis in terms of cognitive and functional decline and mortality (Inzitari et al., 2009). When considered in conjunction with vascular risk factors (such as hypertension, diabetes, and high cholesterol), white matter lesions on MRI predicted a 3.5-fold risk of progression of MCI to all-cause dementia and a 3.8-fold risk of progression to AD (Clerici et al., 2012).

Parkinson's disease

Atrophy in the temporal, parietal and frontal cortices has been reported in patients with MCI in Parkinson's disease (PDMCI) when compared to patients with PD and normal cognition (PDNC) (Klein et al., 2018; Mak et al., 2015; Melzer et al., 2012; Song et al., 2011). Other studies have observed subcortical atrophy, including the hippocampus, thalamus, and nucleus accumbens (Mak et al., 2015; Mak et al., 2014; Weintraub et al., 2011). However, the evidence to date for structural MRI changes in PDMCI remains conflicting, with one notable study of 148 PD subjects finding no significant differences in cortical volumes when comparing PDMCI and healthy controls (Pereira et al., 2012). Neuroimaging biomarkers for the risk of PDMCI conversion to PD dementia continue to be sought.

Lewy body disease

In an initial study of 75 patients with MCI, of which 48 had a clinical diagnosis of possible or probable MCI with Lewy body disease (MCI-LB), (^{123}I)FP-CIT SPECT imaging identified MCI-LB with a sensitivity of 54% and specificity of 89% (Thomas et al., 2019). Low tracer uptake in ^{123}I -metaiodobenzylguanidine (MIBG) cardiac scintigraphy has also been

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suggested in small case series as a potential predictor of progression from amnesic MCI to DLB (Fujishiro et al., 2012). The utility of both modalities of imaging as biomarkers in MCI-LB requires further investigation (Donaghy et al., 2015).

Frontotemporal dementia

Hippocampal atrophy is observed on MRI in patients with established frontotemporal lobar degeneration, with differing patterns of atrophy in its three main clinical subtypes: behavioural variant frontotemporal dementia, semantic dementia, and progressive non-fluent aphasia (van de Pol, 2006; Chan et al., 2001). Studies of genetic FTD have shown that atrophy predates symptom onset and that different atrophy patterns are associated with each mutation, though with a common network of affected regions including the insula, anterior cingulate gyrus, and orbitofrontal cortex (Cash et al., 2018). Of all measured regions, the insula was the first to exhibit volume loss (Rohrer et al., 2015).

A clinician's approach to MCI

History

Patients with MCI typically present with a concern about a decline in episodic memory. Unlike patients presenting with dementia, when insight may be compromised, affected individuals may be able to provide a detailed history of their cognitive difficulties. It is important to be aware that their subjective reporting of symptom severity may be enhanced (if there is underlying anxiety) or diminished (if early AD, i.e. 'forgetting what they have forgotten') and it is critical therefore that a collateral history is obtained from an informant, typically a close friend or relative, and that some objective cognitive testing is undertaken against which to compare the subjective history.

History taking should focus on the types of cognitive problems encountered. It is not uncommon for the patient's report of 'memory' decline to reflect not impairment of episodic memory but instead impairment of attention, naming, or familiar face recognition (prosopagnosia), which may point towards a non-AD diagnosis such as FTD. Questions used to probe episodic memory could include those about recollections of events from day to day, conversations, and appointments. By contrast, symptoms that might indicate a disorder of attention/working memory rather than episodic memory would include misplacing items, defective engagement in everyday functions (e.g. leaving the kettle on accidentally), or transient difficulty in remembering short-term information (e.g. going into a room to perform a task but forgetting what on arrival). There is increasing awareness that spatial navigation can be affected from the earliest stages of AD (e.g. Serino et al., 2014), possibly relating to the role of the hippocampus in spatial memory (Burgess et al., 2002; O'Keefe and Nadel, 1978), and this can be probed with questions about getting lost or impaired sense of direction when driving or walking.

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Executive function can be assessed with queries about problem-solving ability, multi-tasking, and organizational ability. Finally, as well as directed questions evaluating different cognitive functions, the onset (sudden vs gradual) and timescale (duration of symptoms, static vs progressive decline since onset) of cognitive change may be diagnostically informative.

Age-associated cognitive decline is commonplace, and as such the earliest stages of MCI can be difficult to distinguish from healthy ageing on clinical grounds alone. The difficulty of determining the presence of early stage neurodegenerative disease is further complicated by inter-individual differences in cognitive reserve, which leads to the relative preservation of cognition in the context of age and age-related diseases as a result of higher IQ, education, and lifestyle (physical, social, and intellectual) activities. Individuals with high cognitive reserve present a particular diagnostic challenge since they may have early AD but present with minimal cognitive symptoms and have very high scores on cognitive testing. In such instances, careful diagnostic workup, including use of biomarker-based tests, is warranted.

Outside of the cognitive assessment, everyday activities and functions should be evaluated.

A noticeable deficit in the basic activities of daily living (ADLs) would exclude a diagnosis of MCI, but one might elicit subtle deficits in instrumental ADLs (IADLs; Table 29.5). For example, baseline data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) reveals difficulties with remembering appointments, family occasions, holidays, and medications, or assembling tax records, business affairs, or other papers, to be 95% specific in differentiating controls (229 individuals) from a combined group of amnesic MCI (394 individuals) and AD patients (193 individuals) (Brown et al., 2011). While the aMCI patients reported a significantly greater number of functional IADL deficits than controls, the level of severity per deficit was not significantly different between MCI individuals and controls. Extracting this kind of information requires detailed questioning of both patient and informant, but the aim is to establish an overall picture, rather than focus on any single incident.

Table 29.5 Examples of basic and instrumental activities of daily living (ADLs).

Basic ADLs	Instrumental ADLs
• Washing • Grooming (e.g. brushing hair) • Dressing	• Housekeeping and cleaning • Financial management • Food preparation • Medication administration

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• Toileting and continence • Transferring and mobility • Self-feeding	• Grocery shopping • Navigational ability and local mobility (including driving and use of public transport) • Social functioning and communication (including phone or internet use, social interaction, and appointment keeping) • Care of children or pets

Additional questions should focus on sleep (duration of night-time sleep, apnoeic episodes, behavioural disorder during sleep, daytime somnolence), social behaviour, and neuropsychiatric symptoms.

Determination of anxiety is of particular relevance; while anxiety is a common cause of subjective cognitive impairment, it may also be a symptom of prodromal AD. A targeted systems review should be performed, including review of symptoms of the reversible causes discussed above, as well as neurological and psychiatric symptoms including behavioural or personality changes, hallucinations, gait or speech changes, visual or hearing loss, or focal neurological symptoms indicative of other neurological disease. The presence of urinary incontinence and gait disturbance might suggest normal pressure hydrocephalus. Non-AD degenerative disorders may be flagged up on initial history taking; for instance, behavioural, personality, or language change might indicate an FTD syndrome, while visual hallucinations or REM sleep behaviour disorder might suggest Lewy body pathology.

Overall health status should be assessed, including the past medical history and psychiatric history. This includes screening for reversible causes of cognitive impairment, such as depression, anxiety, thyroid disease, nutritional deficiencies, and alcoholism. Cerebrovascular disease, vascular risk factors (smoking, hypertension, diabetes mellitus, dyslipidaemia, and obesity), or cardiovascular disease may suggest an underlying vascular aetiology. A full medication history is necessary, including over-the-counter medications; anticholinergics, antihistamines, opiates, benzodiazepines, and other sedatives (e.g. zopiclone) are just some of the medications that may contribute to impaired cognitive performance. Any family history of young-onset dementia might indicate a genetic disorder whereas a history of late-onset dementia will help determine the level of risk of AD.

Examination

MCI due to AD is not typically associated with any abnormalities on general neurological examination. However, the latter is required to look for clinical signs that might indicate the presence of an alternative underlying cause, such as focal neurological signs or gait apraxia

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(cerebrovascular disease), extrapyramidal signs (Lewy body disease), eye movement disorders (tauopathy), and frontal release signs (FTD).

Cognitive testing

Objective evidence of cognitive impairment is a core component of the diagnosis of MCI, although at present there exists no consensus on the specific cognitive tests to be applied. Cognitive testing can be applied in the form of a general cognitive test, encompassing several cognitive domains; one example is the Addenbrookes Cognitive Examination III (ACE III) (Hsieh et al., 2013). Shorter screening cognitive tests, such as the Mini Mental State Examination (MMSE) (Folstein et al., 1975) or Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) are often used in primary care or domiciliary settings but were designed more for detection of dementia. Caution therefore needs to be exercised in terms of their value in the diagnosis of MCI, as evidenced by a Cochrane review indicating that the MMSE score is a very poor predictor of progression from MCI to dementia (Arevalo-Rodriguez et al., 2015).

Tests of specific cognitive domains are often used to supplement screening general cognitive tests, especially in clinical services where neuropsychological support for memory clinics is available. Given that AD is the commonest underlying cause of MCI, tests of episodic memory are of paramount importance. These can vary in terms of duration and complexity, and current guidelines do not make recommendations for any particular test, though several are namechecked in the 2014 IWG-2 guidelines, notably the Free and Cued Selective Reminding Test (FCSRT) (Buschke, 1984), Paired Associates Learning (PAL) (Barnett et al., 2015) and the Rey Auditory Verbal Learning Test (RAVLT) (Rosenberg et al., 1984). Mention also is made of more recently introduced tests designed around theories of entorhinal cortex and hippocampal function, such as the 4 Mountains Test of spatial memory (Chan et al., 2016; Hartley et al., 2007) and the short-term memory binding test (Pertzov et al., 2012). This overlaps in part with the tests named in the 2011 NIA-AA guidelines, which refer to several verbal learning tests as well as the Logical Memory and Visual Reproduction subtests from the Wechsler Memory Scale (Wechsler, 1987). Tests assessing other cognitive domains include tests of attention and speed of information processing, naming, verbal fluency, and frontal executive function.

In all cases it is important to bear in mind that interpretation of test results needs to take into account background demographic information such as cultural background, premorbid IQ (if available), and years of education. The latter is particularly important, given that results on many cognitive tests are strongly correlated with levels of educational attainment.

In terms of the severity of impairment on cognitive testing required for the diagnosis of MCI, the Mayo Clinic criteria emphasize that diagnosis of MCI is a clinical judgment that neuropsychological tests can support; cut-

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off scores or thresholds for tests are not recommended and clinicians are encouraged to interpret objective test scores in the context of the case at hand. The NIA-AA criteria also do not specify cut-off scores for named cognitive tests, although suggest that as a guideline, MCI patients typically score 1 to 1.5 standard deviations below the mean for their age- and education-matched peers on culturally appropriate data. The DSM-5 criteria for mild neurocognitive disorder similarly indicate that performance typically lies between 1 to 2 standard deviations below the mean in diagnosed cases.

Investigations

Blood tests are performed to investigate possible underlying medical causes, including those that are potentially reversible. As a rough guide, these tests would include full blood count, renal function tests and electrolytes, liver function tests, glucose, thyroid function tests, vitamin B12 and folate, and lipid levels. Syphilis and HIV testing may be indicated in certain clinical contexts. Again, depending on context, more specialized blood tests could include tests for antibodies associated with autoimmune limbic encephalitis, paraneoplastic antibodies, and DNA testing for inherited dementias. Testing for susceptibility genes, such as Apoε4, is not currently recommended as a clinical test.

Brain imaging in the form of a CT or MRI scan is required in order to exclude structural causes of cognitive impairment, such as bleeds, neoplasms, or other space-occupying lesions. Patterns of cerebral atrophy or white matter changes may point towards particular degenerative diseases, although these may be subtle in MCI and qualitative radiological reporting in isolation is very rarely discriminative towards diagnosis in this respect.

Beyond this initial set of assessments and investigations, further testing will be performed at the discretion of the clinician and patient, in the context of local availability. Typically, second-line tests would involve either additional assessment with SPECT or FDG-PET if initial structural imaging is diagnostically uninformative, or biomarkers-based tests for underlying causes (ligand-PET or CSF amyloid/total tau/phosphorylated tau for AD; (¹²³I)FP-CIT or MIBG for DLB). Formal neuropsychological testing may be used to supplement initial clinic-based brief global cognitive testing, in order to look for cognitive profiles pointing towards specific neurodegenerative diseases, or non-degenerative aetiologies such as anxiety, as the underlying cause of MCI.

Management

Medication

To date, clinical studies of potential drug therapies for MCI have been largely negative. There is currently no pharmacological agent that is recommended to reverse MCI or slow its progression to dementia (Petersen, 2016). Cholinesterase inhibitors licensed for the treatment of

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AD dementia (donepezil, rivastigmine, and galantamine) overall have not been found to be efficacious when given in MCI (Doody et al., 2009; Feldman et al.; 2007, Winblad et al., 2008). Comprehensive systematic reviews of published and unpublished data for the use of cholinergic therapies in MCI (Raschetti et al., 2007), and pharmacological therapies at large (Ströhle et al., 2015; Cooper et al., 2013) found no significant difference in the probability of conversion from MCI to dementia between treated and placebo groups. Of non-cholinergic therapies, vitamin E and the anti-inflammatory agent rofecoxib also proved ineffective at slowing progression to dementia.

While reviews to date have concluded that there is no evidence to support the pharmacological treatment of MCI at present, this has to be taken in the context of limitations in terms of the design of previous MCI trials, including: i) the previous inclusion of patients diagnosed with MCI on clinical grounds alone, without biomarker evidence of underlying AD, resulting in an heterogeneous patient cohort; ii) short study durations so consequently low conversion rates from MCI to dementia; and iii) differences between trials in outcome measures used to assess treatment effect. More rigorous trial design and biomarker-based stratification of MCI patients will offset some of these limitations.

New pharmacological targets have emerged over recent years in the search for effective AD therapies, largely focused on β -amyloid given the amyloid hypothesis of AD. To date, phase I and II trials of β -secretase 1 (BACE-1) and γ -secretase inhibitors have proved negative (Mullard, 2017b). The monoclonal antibodies solanezumab, bapineuzumab, and gantenerumab, which bind β -amyloid directly, also missed their primary end points in phase III trials with AD patients (Mullard, 2017a). Aducanumab, had also initially not met its primary endpoints in its phase III trials, although a re-analysis of the trial data suggested that patients receiving a higher dose had a slower decline although at time of writing, this conclusion remains controversial. Nevertheless, Biogen, who own this agent announced plans to apply in early 2020 for regulatory approval for aducanumab in the U.S.

An alternative approach to targeting AD molecular pathology is intervention aimed at the physiological changes in AD. One such trial involved the food supplement, Souvenaid, containing compounds required for brain phospholipid synthesis and shown in animal models to promote synapse formation, cholinergic neurotransmission, and neurogenesis (Janickova et al., 2015; Cansev et al., 2015; Broersen et al., 2013). However, a Souvenaid trial in prodromal AD also did not demonstrate a significant treatment effect in terms of the primary outcome measure, a change in neuropsychological test battery performance at two-year follow up (Soininen et al, 2017).

Non-pharmacological measures

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Cognitive therapy

Epidemiological studies have shown that low levels of education and reduced engagement in cognitively stimulating activities are both independent predictors of subsequent dementia. As a result, there has been great interest in cognitive training strategies that might slow or halt progression of MCI to dementia. However, a systematic review of treatments for MCI (Cooper et al., 2013) found that existing cognitive therapy studies were consistently underpowered to detect differences. The interventions reviewed included computer-assisted cognitive training, and group psychological therapy (consisting of memory training; reminiscence, psychomotor, and recreational tasks; multisensory stimulation; and social interaction). Other reviews (e.g. Stott and Spector, 2011) have raised concerns about the poor methodological quality of cognitive therapy studies, limiting the conclusions that may be drawn from them. Overall, higher-quality, adequately powered studies are necessary to establish whether cognitive training is an effective treatment option for MCI.

Physical exercise

A meta-analysis of exercise interventions in six MCI studies involving 443 patients showed a modest benefit of exercise in slowing progression of MCI (Ströhle et al., 2015), with a further meta-analysis of combined cognitive and physical exercise training in MCI over ten studies also showing a modest improvement in global cognition scores (Karssemeijer et al., 2017). Results, however, remain conflicting: a high-quality randomized trial comparing a year-long programme of twice-weekly group exercise (moderate-intensity walking) with a low-intensity placebo programme (relaxation, balance, and stretching exercises) found no significant difference in cognitive performance in any domain although there was a significant difference in perceived quality of life (van Uffelen et al., 2007). Another high-quality, double-blinded, randomized controlled trial investigated the combined effect of lifestyle interventions in cognitively intact older adults at risk of dementia (Ngandu et al., 2015). There were 1,260 participants between the ages of 60–77 and without MCI, but at high risk of dementia as determined by the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) Risk Score. There was a small but significant effect on cognition in the group randomized to a two-year programme of cognitive training, diet, exercise, and vascular risk-factor modification when compared to the control group. The preventative benefits of combined lifestyle-based interventions in those at risk of MCI and dementia continue to be investigated. As with other interventional MCI studies, the heterogeneity of the MCI study populations affects the interpretation of results, in that it remains unclear if any identified benefits relate to a non-specific cardiovascular benefit, rather than any disease-modifying effect on neurodegenerative pathologies.

Conclusion

From its inception in 1999 to the current day, there has been an evolution in the concept of MCI. Underlying the MCI concept is the notion that it may represent a transitional state between healthy ageing and dementia, and the awareness that it may be caused by a number of different underlying diseases. MCI, identified on clinical grounds alone, describes a heterogeneous patient group that includes those with non-degenerative conditions at low risk of future dementia, such as anxiety. The ability to predict progression from MCI to dementia is therefore dependent on the provision of ancillary information such as biomarker data.

Future years will likely see further refinement of the MCI concept, taking into account not only predictive biomarkers, but also its role in the spectrum from cognitively normal, through to subjective cognitive impairment and ultimately dementia. Greater understanding of MCI and other pre-dementia states will be crucial for the long-term management of the ageing population and the advent of interventions for delaying or preventing the onset of dementia.

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Alzheimer's disease

Chapter: Alzheimer's disease

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Introduction

Alois Alzheimer wrote his original report (Alzheimer, 1907) on a 51-year-old woman (Auguste D) who had suffered an illness involving cognitive impairment and other symptoms including delusions and hallucinations. At post-mortem he described the principal neuropathological features, senile plaques and neurofibrillary tangles, of what we now call Alzheimer's disease (AD). This eponymous term was coined by Kraepelin and was initially restricted to a presenile degenerative dementia. After several decades, Sir Martin Roth and colleagues recognized that older people with identical symptomatology and pathological features had the same disease and, in fact, formed the great majority of cases. AD therefore evolved to become a characteristic clinical syndrome that usually occurs in later life and which is associated with the neuropathological findings described in detail in Chapter 5. The young age of onset in Auguste D has prompted speculation as to whether there may have been an underlying genetic mutation in her case. A 2013 paper

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suggested a presenilin 1 mutation, though this finding has not been subsequently replicated (Muller et al., 2013, Rupp et al., 2014).

AD as a clinicopathological entity has further evolved significantly, particularly in the past ten years. In particular, with the advent of early biomarkers and enhanced aetiological understanding for the basis of AD, there is now a recognition that AD has an extensive preclinical phase which can antedate the onset of dementia by many years.

Alzheimer's disease and the dementia syndrome

Diagnostic criteria for Alzheimer's disease: ICD-10, 11, and DSM-5 criteria

Having confirmed a patient has the dementia syndrome, the next stage is to try to establish the cause. Since AD causes over 50% of all dementia, it has come to be regarded almost as the model for dementia. As such, there was a tendency to diagnose AD by default rather than by the positive identification of the clinical syndrome though this should no longer be the case as biomarkers, imaging, and clinical description of the syndrome have become more sophisticated.

ICD-10 requires that dementia due to AD has an insidious onset and a gradual progression. AD cannot be diagnosed if there is a sudden onset, if there are neurological signs indicating focal brain damage or if the dementia can be explained by other brain or systemic disease. At the time of writing, there is an ongoing revision to ICD and the new DSM-5 diagnostic criteria have recently been published, although these are not the only recently described diagnostic criteria for AD (see Other AD criteria). A key difference between DSM-IV and DSM-5 has been the renaming of the category of the generic 'dementia' syndrome used in DSM-IV to that of 'major neurocognitive disorder'. This change in nomenclature has been driven in part by the ongoing debate of the utility vs pejorative associations of the word 'dementia' as well as the prior tendency to always associate 'dementia' with Alzheimer's when there are, of course, many causes of dementia (Sachdev et al., 2015). More specifically and relevant to this chapter, the DSM-5 criteria now include a diagnosis of major or mild neurocognitive disorder, of which AD is one subtype. Mild neurocognitive disorder is used in recognition that less severe cognitive impairment can occur and thus might allow for earlier diagnosis. In addition, mild cognitive disorder as an umbrella diagnosis can include cases where the cognitive impairment is non-progressive (e.g. due to head injury) rather than progressive. These criteria overlap with definitions of mild cognitive impairment (MCI) (Chapter 29) where patients are still maintaining their functional independence, although for a diagnosis of mild cognitive disorder due to probable AD, DSM-5 criteria demand that there has to be the presence of a causative AD-related genetic mutation given the high degree of uncertainty that exists in the diagnosis of AD in the very early stage. There are more flexible diagnoses for both major and mild neurocognitive disorder, i.e. possible AD is

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accommodated if key criteria are not met, including lack of evidence of a decline in memory and learning as well as at least one other cognitive domain, unclear progression with either atypical declines or extended plateaus, or the suggestion that the cognitive impairment is secondary to mixed aetiologies.

DSM-5 includes the recognition that comorbidity is the norm and that having cerebrovascular disease does not preclude an individual also having AD, or vice versa. Indeed DSM-5 can accommodate mixed aetiologies (e.g. vascular and AD) by listing each under a separate diagnostic heading. Similarly, while typical presentations are amnesic, the new criteria accept that memory loss is not an absolute criterion for the major neurocognitive disorder due to AD; other presentations with prominent visuospatial deficits or logopenic aphasia are accepted variants. In addition, the separation between early and late onset that was present in DSM-IV has been removed, given the lack of scientific validity in this arbitrary distinction. Finally, criteria also consider the presence and absence of behavioural symptoms (e.g. depression, apathy, psychosis, etc.) as well as the severity of functional deficits that range from impairments in only instrumental activities of daily living (ADLs) (mild) such as managing money through to impairments in basic ADLs such as dressing/feeding self (moderate) and then to total dependency (severe).

ICD-10 was endorsed in May 1990. An early version of ICD-11 was released in June 2018 to allow preparation for transition with anticipated ratification in 2019 and changes to reporting from 2022. The advance online ICD-11 description for dementia retains many of the features from ICD-10 and describes a decline in previous level of function in at least two cognitive domains which significantly impairs independence or ADLs and arises from a condition affecting the brain. The conditions listed include trauma, which suggests the possibility of dementia encompassing relatively fixed deficits in contrast to the description of dementia being usually 'chronic or progressive' in ICD-10. The diagnostic description of Alzheimer's disease in ICD-11 recognizes the early appearance of memory symptoms and progression to include other cortical cognitive domains as well as the common occurrence of other mental and behavioural symptoms, many of which are included as sub codes.

Other recent Alzheimer's disease criteria

Both the ICD-10 and DSM-5 criteria for AD are related to the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association) criteria. The original 1984 NINCDS-ADRDA criteria (McKhann et al., 1984) have been shown to have a sensitivity and specificity for AD of over 80% (Burns et al., 1990f; McKeith et al., 2000a) and have very good inter-rater reliability (Farrer et al., 1994), but they have now been superseded by the revised 2011 criteria (McKhann et al., 2011). In the intervening years since the original criteria, our understanding of the

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pathophysiology and clinical progression has advanced and, as a result, there have been recent and, indeed, necessary reconsiderations of the diagnostic criteria for AD: the Working Group for New Research Criteria for the Diagnosis of Alzheimer's Disease led by Bruno Dubois (Dubois et al., 2007, 2010) and the revised McKhann criteria from the Alzheimer's Association (AA) and National Institute on Aging (NIA) (McKhann et al., 2011). While there are notable differences between these two diagnostic systems and ongoing debate regarding the most appropriate nomenclature, within these new criteria there is now an emphasis on how one defines Alzheimer's as a disease process and a focus on classification of Alzheimer's before the emergence of the dementia, with increasing prominence given to biomarkers from cerebrospinal fluid (CSF) and neuroimaging.

International Working Group for New Research Criteria for the Diagnosis of Alzheimer's Disease

The criteria proposed by Dubois and colleagues (2010) seek to establish a new nosological lexicon for AD by dividing it into three categories: 'preclinical stages of AD', 'prodromal stages of AD', and 'AD dementia'; these categories represent a continuum from individuals who evidence the presence of AD pathology as evaluated using biomarkers (coined 'symptomatic at risk'), or who have a genetic mutation that makes eventual AD dementia a certainty (defined as 'pre-symptomatic AD') but who do not currently have any cognitive or behavioural symptoms, through to individuals with mild symptoms and biomarker evidence of AD pathology but who do not reach the threshold for AD dementia diagnosis, and finally to those who have frank and symptomatic AD dementia. Chapter 29 describes in detail the 'preclinical stages of AD' and 'prodromal stages of AD', whereas the different lexical concepts of AD dementia including typical, atypical, and mixed AD dementia proposed by Dubois and colleagues (2007) are described here:

Typical AD: This refers to the most common clinical presentation of AD which is characterized by an early significant and progressive episodic memory deficit that remains dominant in the later stages of the disease, and is followed by or associated with other cognitive impairments (executive dysfunction, language, praxis, and complex visual processing impairments) and neuropsychiatric changes. The emphasis on episodic memory deficits or amnesic syndrome of the hippocampal type as a core feature arises from empirical evidence that the medial temporal lobes are typically the first structure affected by AD pathology before it cascades to other cortical areas. The criteria also allow for further support for the diagnosis of 'typical AD' by the presence of one or more AD biomarkers (Box 30.1).

Box 30.1 Alzheimer disease biomarkers

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In the Dubois and colleagues (2007) criteria, biomarkers are divided into pathophysiological and topographical markers.

Pathophysiological markers relate to known degenerative processes that are associated with AD, including amyloid deposition

(particularly amyloid 1-42 beta) and the presence of abnormal tau.

Topographic markers relate to the subsequent impact of these cellular pathological changes, such as structural atrophy in the medial temporal lobe and reduced metabolism in temporoparietal regions on PET FDG imaging.

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Atypical AD: This term is used to describe less common variants of AD, including syndromes such as progressive non-fluent aphasia, logopenic aphasia (characterized by slow speech and word-finding difficulties), frontal variant of AD, and posterior cortical atrophy; however, as these syndromes also map onto other differential diagnoses (e.g.

frontotemporal dementias) the criteria demand that the diagnosis of AD is supported by presence of amyloid in the brain (tested using, for example, amyloid labelled radioligands) or CSF changes characteristic of AD.

Mixed AD: This is used in the criteria to include individuals who meet the 'typical AD' criteria but who additionally have evidence (e.g. clinical, imaging, or biological) of other conditions that could be causing their dementia, such as cerebrovascular disease or Lewy body disease. Thus, one might consider mixed AD if there was a history of parkinsonism, gait disturbance, hallucinations, cognitive fluctuations, recent or past history of stroke, or evidence of small vessel ischaemic change or infarcts on neuroimaging. However, it is important to note that the presence of these symptoms or signs does not equate to an assumption of mixed aetiology. Indeed, Dubois and colleagues propose that, in the case of mixed AD and cerebrovascular disease, there must be both a history of stroke and imaging signs of cerebrovascular disease.

NIA/AA diagnostic criteria

The new NIA/AA guidelines for the diagnosis of AD, envisaged as a replacement to the 1984 NINCDS-ADRDA criteria (McKhann et al., 1984), are not dramatically different from the original criteria, although there is a recognition in that other forms of dementia such as dementia with Lewy bodies (DLB), vascular dementia (VaD), and frontotemporal dementia (FTD) have distinguishing and different clinical features that were not defined in the NINCDS-ADRDA criteria. As such, the NIA/AA guidelines have overarching diagnostic criteria for all dementias (defined as all-

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cause dementia) as well as specific criteria for dementia caused by Alzheimer's. Finally, there is an awareness in the guidelines that genetics and biomarkers have a role in increasing the certainty of the diagnosis. Table 30.1 shows a summary of the classification of dementia due to AD by these guidelines. All-cause dementia is diagnosed (a prerequisite before considering the diagnosis of AD) when there are cognitive or behavioural symptoms that:

1. interfere with the ability to function at work or at usual activities;
2. represent a decline from previous levels of functioning and performing; and
3. are not explained by delirium or major psychiatric disorder.

Table 30.1 NIA/AA diagnostic criteria.

Probable AD dementia: Core clinical criteria	
	Meets criteria for dementia (discussed in text) and, in addition, has the following characteristics: A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days; B. Clear-cut history of worsening of cognition by report or observation; and, C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories: i) Amnestic presentation: it is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, e.g. impaired reasoning and handling of complex tasks or impaired visuospatial ability) ii) Non-amnestic presentations: • Language presentation: the most prominent deficits are in word-finding. • Visuospatial presentation: the most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia.

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	• Executive dysfunction: the most prominent deficits are impaired reasoning, judgment, and problem solving. <i>Note:</i> for each presentation, deficits in other cognitive domains should also be present. D. The diagnosis of probable AD dementia should not be applied when there is evidence of: i) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or ii) core features of DLB other than dementia itself; or iii) prominent features of behavioural variant FTD; or iv) prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia; or v) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity, or use of medication that could have a substantial effect on cognition.
Probable AD dementia with increased level of certainty	
Probable AD dementia with documented decline	Evidence of progressive cognitive decline on subsequent evaluations based on information from informants and cognitive testing in the context of either formal neuropsychological evaluation or standardized mental status examinations.
Probable AD dementia in a carrier of a causative AD genetic mutation	Evidence of a causative genetic mutation (in APP, PSEN1, or PSEN2) increases the certainty that the condition is caused by AD pathology.
Possible AD dementia: Core clinical criteria	

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Possible AD dementia with atypical course	Atypical course meets the core clinical criteria in terms of the nature of the cognitive deficits for AD dementia, but either has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline.
Possible AD dementia with aetiologically mixed presentation	Meets all core clinical criteria for AD dementia but has evidence of: i) concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or ii) features of DLB other than the dementia itself; or iii) evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition.
Probable AD dementia with evidence of the AD pathophysiological process	
	Diagnosis made in persons who meet the core clinical criteria for probable AD and who have biomarker evidence of AD pathophysiology, which increases the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process. Biomarkers include those described in Box 30.1
Possible AD dementia with evidence of the AD pathophysiological process	
	Reserved for people with clinical criteria for a non-AD dementia but who either have biomarker evidence of AD pathophysiological process or meet the neuropathological criteria for AD.
Pathophysiologically proved AD dementia	
	Meets the clinical and cognitive criteria for AD dementia outlined earlier in the text, and the

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	neuropathological examination, using widely accepted criteria (Hyman and Trojanowski, 1997).
Dementia unlikely to be due to AD	
	A. Does not meet clinical criteria for AD dementia. B. i) Regardless of meeting clinical criteria for probable or possible AD dementia, there is sufficient evidence for an alternative diagnosis such as HIV dementia, dementia of Huntington's disease, or others that rarely, if ever, overlap with AD. ii) Regardless of meeting clinical criteria for possible AD dementia, both amyloid and neuronal injury biomarkers are negative.

Adapted with permission from McKhann, G. M., et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging- Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7(3): 263-9. Copyright © 2011 Published by Elsevier B.V. <https://doi.org/10.1016/j.jalz.2011.03.005>.

The guidelines suggest that the cognitive impairments should be diagnosed by taking a history from both the patient and an informant as well as carrying out an objective cognitive assessment. The NIA/AA guidelines demand that the cognitive or behavioural impairment includes a minimum of two domains (memory, executive, visuospatial, and language function; changes in personality, behaviour, or comportsment).

Summary: AD diagnosis

At the time of writing, we are currently in a state of flux with regard to how AD is diagnosed. This probably represents a 'paradigm shift' in how we clinically view the condition and how it will be treated in the future. Overall, there are significant overlaps between the new emerging diagnostic criteria, which share an emphasis on earlier diagnosis, that is, with a view to the development of disease-modifying treatments which would need to be given as early as possible in AD.

One challenge with the DSM-5 criteria is a lack of biological focus and no specific inclusion of biomarkers aside from family history and/or evidence of AD related genetic mutations.

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Choice of which criteria are used may depend upon clinical speciality, local regulatory requirements, and familiarity, although overall while there are still differences between the various AD criteria, there is an increasing convergence of opinion (Morris et al., 2014). It seems likely that diagnostic criteria in the future will increasingly incorporate biomarkers as these are being continually refined with increased sensitivity and specificity.

Assessment

Regardless of whether we apply the ICD-10 or DSM-5 criteria, accurate assessment and diagnosis requires a systematic and thorough assessment: a full history (including from an informant), mental state examination, cognitive examination, physical assessment (including neurological examination), and investigations. The latter are important because alternative causes include both systemic diseases, e.g. vitamin B₁₂ deficiency and hypothyroidism, and brain diseases, e.g. normal pressure hydrocephalus and stroke. Box 30.2 shows a list of common investigations.

Box 30.2 Common investigations in dementia and Alzheimer's disease

- Full blood count
- Urea, creatinine, and electrolytes (including calcium)
- Liver function tests
- Thyroid function tests
- Vitamin B12 and folate
- Blood Glucose or HbA1c
- CT/MR scan of head to exclude other structural causes, to assess for level of vascular pathology, and to look for the extent and pattern of atrophy, looking particularly for medial temporal atrophy in AD

Additional investigations which may be appropriate in some cases include:

- Urinalysis
- HIV/syphilis serology
- Genetic testing for autosomal dominant genes leading to AD or those leading to other neurodegenerative diseases, e.g. FTD, CADASIL, or Huntington's disease
- Further imaging, including: SPECT hexamethylpropyleneamine oxime (HMPAO) or PET fluorodeoxyglucose (FDG) scan or Amyloid PET or ¹²³I-FP-CIT SPECT (FP-CIT SPECT) if DLB is a possibility.

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- EEG
- Lumbar puncture including analysis for Alzheimer's proteins
- Detailed neuropsychological testing

Note: Conditions such as hypothyroidism and mild vitamin B12 deficiency are common and when they are detected by routine tests this does not necessarily indicate they are making a complete causal contribution to the cognitive problems.

The identification of C-11 labelled Pittsburgh Compound B provided the opportunity for in vivo identification of cerebral amyloid and therefore a possible biomarker for helping to diagnose AD (Klunk et al., 2004). Subsequently, more stable ligands have been identified which can do a similar job and studies in research participants have demonstrated potential usefulness as a diagnostic tool. However, a number of features make it more difficult to apply to clinical settings. One of these is that the incidence of positive amyloid scans increases with age. Half of those over 80 have a positive scan, but not all are demented (Rowe et al., 2010). There are also difficulties with 'false positives' in other dementing conditions (e.g. DLB) and also difficulty in distinguishing the exact nature of amyloid deposition. Nevertheless, this is a welcome potential extra tool in making what can be a difficult diagnosis, and consensus guidelines for use are beginning to appear (Johnson et al., 2013).

A further potential new diagnostic tool is analysis of CSF for A β 1-42, total tau (T-tau), and phosphorylated tau (P-tau). Amyloid concentrations in the CSF decrease with disease progression while tau and phosphorylated tau increase. This allows for the calculation of the ratios between these proteins to enhance diagnostic accuracy. Reported sensitivities and specificities have exceeded 90% and studies now include autopsy-confirmed cases (Engelborghs, 2008). However, much as with amyloid imaging, the specificity of CSF biomarkers decreases with age. Around a third of cognitively normal people aged 85 will have an abnormal result, and other degenerative diseases of the nervous system, including stroke and other forms of dementia, can also lead to an abnormal result. Clinical guidelines for these tests are also now emerging. For example, analysis of CSF for these proteins is included in the most recent NICE guidelines as an alternative to functional PET/SPECT scanning in cases where diagnosis is uncertain (<http://www.nice.org>).

Differential diagnosis

Historically, the biggest differential for AD among people with dementia was VaD. Understanding of the relationship between AD and VaD has evolved due to large pathological studies. These have demonstrated that vascular and Alzheimer pathologies become more common as we age and

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increase the risk of dementia, but equally that some older people have pathologies associated with dementia, including AD, but do not show the clinical syndrome and so the correlation between pathology and dementia decreases with age (Saava et al., 2009). These pathological data correlate with the sensitivity of biomarkers and with clinical experience, so at younger age a relatively confident clinical diagnosis of dementia subtype can be made, but as age advances dementia is frequently mixed in origin. ICD-10 allows for a double diagnosis of AD and VaD, and new NIA/AA guidelines have a category of mixed dementia to include individuals who have cerebrovascular disease (stroke related to the onset/worsening of the dementia or evidence of severe white matter hyperintensities or infarcts on neuroimaging) but who also meet the core criteria for a diagnosis of AD dementia. As mentioned, the DSM-V criteria allow for an individual to have both a major/minor neurocognitive disorder due to AD as well as a major/minor neurocognitive disorder due to VaD.

Such a diagnosis should be made when there is clear evidence of each disease process contributing to the dementia, e.g. someone with AD who subsequently has a stroke and suddenly declines cognitively. However, a note of caution also needs to be given with the advance in neuroimaging methodologies, particularly magnetic resonance imaging: the mere presence of mild small vessel disease, lesions that are common even in non-cognitively impaired older people, should not be taken as evidence for a vascular contribution to the dementia. Indeed, in the AD criteria developed by Dubois and colleagues (2007), merely having white matter changes on imaging without any obvious neurological signs (e.g. motor or gait disturbance) cannot be used as a basis for making a diagnosis of mixed AD. Furthermore, more recent neuropathological studies have challenged the view that the changes regarded as being due to small vessel disease are purely vascular in origin, but instead might also relate to the Wallerian axonal degeneration that occurs in AD (McAleese et al. 2017).

A further major differential diagnosis for the dementia syndrome in older people is DLB, which is covered in Chapter 32. Post-mortem data suggest that DLB is a more common cause of dementia than previously appreciated, though the lower rates of clinical diagnosis (only some 7.5% of all dementia cases even in secondary care) suggests cases may be incorrectly attributed to other pathology (Rizzo et al., 2018). In the recently revised consensus criteria for DLB (McKeith et al., 2005, revised 2017), it can be diagnosed confidently (probable DLB) in the presence of at least two of the four core features (recurrent visual hallucinations, fluctuation, REM sleep behaviour disorder, and spontaneous parkinsonism), or one core feature plus one indicative biomarker (REM sleep without atonia as confirmed on polysomnography, dopaminergic abnormalities in the basal ganglia on functional neuroimaging, or abnormal (low uptake) of ¹²³iodine-MIBG on myocardial scintigraphy). However, when only one of these core features is found (without indicative biomarker evidence) or one or more of the biomarkers is

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present but there are no core clinical features, possible DLB may be diagnosed (McKeith et al., 2017), although subjects may meet criteria for possible AD (McKhann et al., 1984) as well. Cognitive fluctuation can occur in AD (particularly in moderate and severe dementia) and visual hallucinations are also found (see Clinical features of Alzheimer's disease), so the presence of these features does not necessarily preclude a diagnosis of AD. The situation can often become clearer over time: the development of parkinsonism in the earlier stages favours a DLB diagnosis, but parkinsonism due to Alzheimer pathology in the substantia nigra is common in more severe dementia, whereas if delusions, hallucinations, apathy, and agitation are less persistent and improve (McKeith et al., 2000b,c) over time without treatment, this makes AD more likely. Making a diagnosis of DLB as opposed to AD has important clinical implications. For example, the former often responds better to cholinesterase inhibitors and DLB patients can have serious adverse reactions to neuroleptics.

In younger patients, FTD should be considered, especially if frontal features are prominent, e.g. primitive reflexes, disinhibition, marked apathy, or disproportionate impairments in executive compared to memory function. This is dealt with in Chapter 33.

Summary: AD diagnosis

The diagnosis of AD is a two-stage process. First, clinical evidence for the dementia syndrome is gathered, and other illnesses such as depression and delirium are excluded, and then the presentation is examined to see if it fits the above AD criteria of insidious onset and gradual progression in the absence of other possible causes with a common early hallmark of impaired short term memory. The two main other causes to consider in older people are VaD and DLB. Usually a careful assessment allows such distinctions to be made, but sometimes the clinician needs to wait patiently for further evidence as the disease progresses. Such distinctions are important because depression and delirium clearly merit a different kind of treatment from any cause of dementia.

Clinical features of Alzheimer's disease

Cognitive symptoms

These are central to the concept of dementia and AD. Cognitive symptoms and their assessment and treatment are dealt with in detail elsewhere (see Chapter 10, Chapter 35, and Chapter 36). Here we describe only the key symptoms and their progression as they are usually encountered in AD in clinical practice. (Note: here we use aphasia and dysphasia synonymously, although strictly speaking the former refers to complete impairment of language and the latter to partial impairment. The same applies *mutatis mutandis* to apraxia/dyspraxia, alexia/dyslexia, and agraphia/dysgraphia).

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Amnesia

Memory impairment is the classic presenting complaint for AD, although other symptoms, e.g. apathy, subtle personality changes, and dysphasia, are often found early in the illness, too. The amnesia typically presents with a history of misplacing and losing objects, forgetting appointments, or repeatedly asking the same question. At this early stage, working memory (e.g. the ability to repeat back a few words or a list of numbers) is relatively unimpaired. However, the ability to recall such words or numbers a few minutes later is significantly impaired because the earliest deficits in AD are in the process of encoding or laying down new information in the memory stores. This probably results from damage to the hippocampal formation, which is the site of the earliest pathological damage in AD, hence the importance that is now attached to episodic memory dysfunction as a core feature in the newer diagnostic criteria for AD. Early hippocampal involvement is also behind early difficulties with spatial memory, remembering where items have been left, and navigating initially outside, but later in the disease also inside the home. Failure to lay down new memories can be demonstrated more clearly by tests in which a patient is read a short story and asked to recall it (logical memory tests) or when a long list of words is read and repeated attempts are made to learn the list, e.g. Rey Auditory Verbal Learning Test, and tests of verbal episodic memory are now part of National Institute for Health and Care Excellence (NICE) guidelines for the assessment of AD (NICE, 2018; <http://www.nice.org>).

In the early stages of AD, the recall of previously learned information remains good, showing that memory retrieval processes remain intact. This pattern results in the typical pattern of a failure of new learning (no memory for recent events) combined with clear memories of events earlier in life. Some individuals, particularly those with high intellectual reserve, can compensate for these deficits and others make use of memory prompts/cues such as diaries or making notes, and thus minimize, at least in the early stages, the impact of disease. However, as AD progresses, the memory impairment broadens to include retrieval of older memories and these are typically lost according to Ribot's law (more recent information is lost before more remote events), so the patient appears to live in the ever more distant past, for example, thinking that they still have young children or that their own parents are still alive. As well as these losses in episodic memory (personally related events occurring in a specific situation) there are accompanying losses in semantic memory (facts and vocabulary) and visuospatial memory.

Aphasia (dysphasia)

Deficits in cortical language production are usually present in the early stages of AD if the patient is examined closely. The earliest manifestation is with word-finding difficulties, where the patient struggles from time to time to find the correct words to complete sentences. Attempts to cover this up by using circumlocutions are common and may be cleverly

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executed by intellectually more capable patients so the deficits are hidden. At this time there is also usually impairment in the naming of objects (nominal aphasia), which will initially be for the names of less common items rather than the more common objects that are frequently tested, e.g. pen or watch. Thus, pointing at objects in the room, e.g. a television, or parts of objects, e.g. the winder on a watch, may show some nominal aphasia that would not otherwise be revealed. As AD progresses, these deficits worsen and problems in the comprehension of language develop (receptive dysphasia) and expression of language shows syntactical errors, circumlocutions, and simplification of sentence structure. Phonemic (the substitution of similar sounding words) or semantic (the substitution of words with related meaning) paraphasias may be seen. Manifestation of language difficulties earlier in the presentation may raise the suspicion of alternative disease aetiologies, e.g. semantic dementia (see Chapter 33). Verbal perseveration, in which the patient repeats the same answer to consecutive questions, may now occur, too. The development of these deficits has serious consequences, as patients now increasingly struggle to understand what is going on around them and to communicate their confusion and distress clearly to others. It should not be assumed that a concurrent loss of all understanding occurs, as patients may still be sensitive to emotional and other nonverbal cues.

As the dementia becomes severe, marked poverty of the content of speech develops, with the repetition of short simple sentences on favourite themes and, eventually, mutism may occur. Some patients babble meaningless sounds or repeat words or part of words (palilalia and logoclonia) and phrases they hear (echolalia). Progression in language deterioration is not inevitable and many patients remain superficially fluent. They maintain a social discourse that can deceive the unwary about the true extent of their cognitive impairment. Careful attention to their language comprehension and production, however, will usually reveal a pattern of language impairment, including the deficits described.

Apraxia (dyspraxia)

Dyspraxia is the failure to carry out complex motor tasks due to deficits in the higher cortical control of movement, and *not* because of damage to the peripheral sensory or motor systems or in coordination. It typically occurs with cortical deficits in the dominant (usually left) parietal lobe, but as with other cognitive symptoms in dementia, dysfunction in other areas is also usually present. Ideomotor apraxia is the form usually elicited on examination and refers to the inability of the patient to carry out a motor task to command. Examples include: asking patients to wave; demonstrate how they brush their teeth; blow out a match; or show how they comb their hair.

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Other common 'dyspraxias' described in clinical practice include dressing dyspraxia and constructional dyspraxia. Strictly speaking, these are not dyspraxias as they are not necessarily due primarily to higher motor failure. Dressing dyspraxia refers to the common difficulty patients have in putting their clothes on correctly due to faulty visuospatial processing, which results in them being unable to orientate their body properly in relation to their clothing. It is usually taken to indicate right (nondominant) parietal lobe damage. Constructional dyspraxia refers to the failure to adequately reproduce a two- (or three-) dimensional drawing, e.g. a star or a clock, or to the similar failure to assemble blocks into the required model. Like dressing, such tasks actually involve multiple cognitive domains (visual, spatial, executive, sensory, motor), but failure is usually taken to indicate right (non-dominant) parietal damage. All these dyspraxias have dire consequences for the patient's ability to carry out many ADLs. Cooking, cleaning, and general housework require the ability to carry out motor sequences, as do more basic activities such as eating and using the toilet. Failure in such domains is not primarily due to memory but to dyspraxic losses. Relatives may misunderstand why someone who appears healthy apart from an apparently mild memory impairment should struggle in such areas, and explaining the global nature of dementia can help them understand the situation.

Agnosia and visuospatial dysfunction

Agnosia is the failure to correctly interpret a sensory input in the presence of an intact sensory system and it is common in AD. Like apraxia, it is due to cortical damage and can occur in any sensory modality, though visual agnosia is the form usually met in clinical practice. In visual agnosia a patient sees an object but does not recognize it. Common agnosias include failure to recognize objects around the house, e.g. mistaking the kettle for the teapot or the dustbin for the toilet, and these, too, can have serious consequences for the patient. Perhaps the most well-known is prosopagnosia, in which the patient fails to recognize a familiar face, and when the face is that of a relative it can be very distressing for all concerned. Other variants include the 'mirror sign'—an inability to recognize oneself in the mirror—and there is considerable overlap between these misidentification phenomena and those more typically seen where the misinterpretations are elaborated by paranoid delusions (see Delusions).

Related to visual agnosia is the occurrence of visuospatial difficulties ranging from copying difficulties through to recognizing whole objects (agnosia). Right/left disorientation can also occur in AD and may be detected by asking the patient to obey commands such as 'point to the left ear with the right forefinger'. It is important to be aware that disproportionate visuospatial difficulties compared to the global cognitive state may be indicative of a non-AD presentation, e.g. posterior cortical atrophy or DLB (see Chapter 32).

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Frontal-executive dysfunction

Damage to the frontal lobes has profound effects on personality, mood, and behaviour (discussed later). Cognitive effects include inflexibility in thinking and difficulties in problem-solving, abstraction, planning, and correctly sequencing behaviour. This is a complex area but one that should nonetheless be tested during assessment of dementia. It is dealt with in more detail in Chapter 10. Proverbs have traditionally been used to test how concrete and inflexible someone's reasoning is, but they are often very difficult to interpret. 'Similarities and differences' tests involve asking the patient what two objects (e.g. table and chair; shoe and boot) have in common and how they differ. Again, these can be difficult to interpret, but some attempt should be made, especially in someone who appears frontally impaired (e.g. markedly disinhibited). Easier to interpret are verbal fluency tests of frontal lobe function. These involve asking patients to name as many objects in a category in one minute (e.g. fruit or animals) or asking them to generate as many words as they can think of beginning with the same letter in one minute (e.g. F, A, and S in 'the FAS test'). As a rough guide, a normal subject should produce more than 15 words for each in a minute, and fewer than ten is clearly abnormal. A third kind of frontal test involves testing the subject's ability to shift from one item to another and this reveals perseverative problems. A sequence of alternating shapes or numbers may be written and the patient asked to continue the sequence. Motor perseveration can be demonstrated using the Luria two-step or three-step tests (in which the subject is asked to copy the examiner in alternately opening and closing the hand or making a fist, then an edge, and then a palm, respectively). In someone who shows any of these 'frontal' features physical examination can be undertaken for 'primitive reflexes' (see section Physical symptoms—neurological).

Executive dysfunction can arise early in the course of AD and is a common symptom with one study finding executive dysfunction in nearly two-thirds of AD patients (Swanberg et al., 2004). However, an early presentation of these symptoms in excess of memory difficulties, particularly in younger patients, should raise the suspicion of non-AD causes, such as FTD.

Other cognitive deficits

Corresponding to the aforementioned deficits in spoken language are impairments in reading (dyslexia) and writing (dysgraphia), which can be often identified with simple tests in AD using pen, paper, and reading material. Acalculia (more accurately anarithmetria) is the loss of the ability to do simple sums and can similarly be tested for in a straightforward way.

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Neuropsychiatric and other non-cognitive symptoms

In his original report, Alois Alzheimer (1907) described both delusions and hallucinations in his patient Auguste D. The emphasis on the cognitive symptoms of dementia in making the diagnosis can distract from the fact that neuropsychiatric symptoms are very common; indeed, these symptoms tend to increase over time and almost all AD patients are affected by at least one neuropsychiatric symptom during their illness (Jost and Grossberg, 1996; Lyketsos et al., 2002; Steinberg et al., 2008; Zhao et al., 2015).

A systematic review and meta-analysis by Zhao and colleagues (2015) of 48 studies that reported prevalence data for the Neuropsychiatric Inventory (NPI) subscales (Box 30.3) found that the most frequent neuropsychiatric symptom was apathy, followed by depression, aggression, anxiety, and sleep disorder. Less common neuropsychiatric symptoms were irritability, appetite disorder, aberrant motor behaviour, delusions, and disinhibition, with hallucinations with euphoria the least reported symptom. One challenge from this meta-analysis was the wide variation in prevalence estimates between studies and differences in populations sampled with the majority being cross-sectional and clinic based.

Box 30.3 Prevalence of neuropsychiatric symptoms in Alzheimer's disease with 95% confidence intervals (in brackets)

Psychotic

Delusions 31% (27–35%)

Hallucinations 16% (13–18%)

Mood

Depression 42% (37–46%)

Anxiety 39% (32–46%)

Euphoria 7% (5–9%)

Behavioural

Apathy 49% (41–57%),

Aggression 40% (33–46%)

Appetite change 34% (27–41%)

Aberrant motor behaviour 32% (25–38%)

Disinhibition 17% (12–21%)

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Sleep disorder 39% (30–47%)

Irritability 36% (31–41%)

Source: data from Zhao Q et al. (2015). The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *Journal of Affective Disorders*, 190, 264–71.

Overall lifetime rates of neuropsychiatric symptoms are much higher and the Cache County prospective longitudinal study (Steinberg et al., 2008) has provided up to five-year period prevalences for some of the major symptoms (Fig. 30.1).

Box 30.4 Pharmacological management of aggression, agitation, and psychosis in dementia

While this box focuses on the management of aggression, agitation, and psychosis in AD, many of these points are applicable to other neuropsychiatric and behavioural disturbances that are found in dementia.

- Consider, first, if nonpharmacological and social care interventions can solve the problem. In this context, taking a multidisciplinary approach and involving occupational therapy, nursing and social care staff can help.
- Always ask why is this patient presenting with this symptom now? Is there a treatable cause for his/her behavioural disturbance (e.g. pain, constipation, urinary retention)?
- Before instituting any pharmacological treatment always discuss with patients, carers and relatives the rationale for prescribing and discuss any potential harms associated with the medication (e.g. stroke and mortality risk with antipsychotics).
- Perform baseline assessment of the nature, frequency, and severity of the behavioural disturbance to compare against future changes in presentation.
- If symptoms persist or are severe in nature with a potential risk of harm (to themselves or others), consider a cautious trial of an antipsychotic.
- Benzodiazepines may be considered in certain specific circumstances if behaviour is severely disturbed and/or has an anxiety focus or if DLB is a diagnostic possibility, but be alert for excess sedation, worsening cognition and falls.
- Alternative medications include use of citalopram (possibly effective in agitation) or trazodone (possesses sedative qualities).

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in addition to antidepressant effect which may help with some individuals with sleep difficulties (Camargos et al. 2014)).

- For all medications:
 - Start low and go slow
 - Review use of the drug regularly, balancing side effects and response
 - For antipsychotics, be aware that most neuroleptic reactions occur in the first two weeks, and if parkinsonism manifests consider a diagnosis of latent DLB and stop the antipsychotic
 - Do not prescribe drugs for prolonged periods. Regularly reassess the need for the drug; can alternative interventions be applied now the situation is containable? Antipsychotics can usually be stopped without re-emergence of behavioural disturbance.

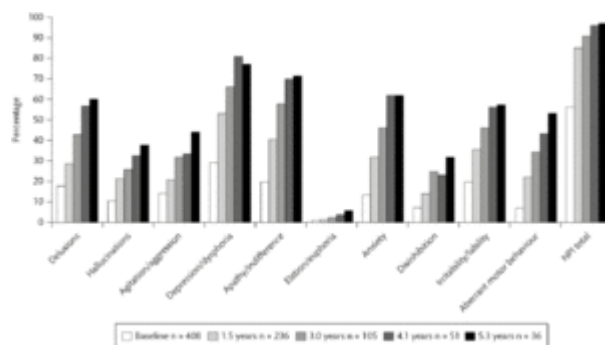


Fig. 30.1

Period prevalence of neuropsychiatric symptoms in AD from the Cache County prospective longitudinal study over a five-year period.

Reproduced with permission from Steinberg, M., et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *International Journal of Geriatric Psychiatry*, 23(2): 170-7. Copyright © 2007 John Wiley & Sons, Ltd. <https://doi.org/10.1002/gps.1858>.

However, accurately eliciting these mental state phenomena can be difficult in people with dementia and the figures quoted in following sections and in Box 30.3 and Fig 30.1 are derived from interviews with informants, who may overrate some symptoms (e.g. depression) compared with trained observers (Burns et al., 1990d). The rates of all the neuropsychiatric symptoms vary widely depending on, among other things, how the phenomena are defined, which patients are sampled, and the timeframe over which the survey is conducted. It is worth noting that

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many of the studies were conducted before the accurate recognition of DLB was possible, which has a much higher rate of psychosis, and so the figures for AD are likely to be inflated by an admixture of DLB patients.

Associations between the manifestations of neuropsychiatric symptoms in AD with the level of cognitive impairment are not consistent, although some symptoms such as apathy (Onyike et al., 2007) and irritability (Craig et al., 2005) appear to be associated with the degree of cognitive decline. Other symptoms such as psychosis may predict accelerated cognitive decline (see Psychotic symptoms for further discussion).

Finally, it is important to recognize that other non-cognitive symptoms such as physical and neurovegetative symptoms have a profound impact upon patients with AD and their care.

Psychotic symptoms

Delusions

Delusional beliefs are common, can be very distressing to carers, and may contribute to early institutionalization. They are often understandable as attempts by patients to make sense of their situation and include beliefs that objects have been stolen, a spouse is unfaithful, or that intruders have been in the house. These beliefs commonly have a persecutory flavour and tend to lack the complexity and systemization of the delusions seen in schizophrenia. The delusions are often short-lived and can therefore be difficult to distinguish from confabulations. For hospital patients, the prevalence of delusions in published studies varies from about 25% (Cooper et al., 1991) to about 50% (Hirono et al., 1998). Burns and colleagues (1990b) studied a sample of AD patients in a catchment area and found 16% had delusions at some point in their illness and 11% had them in the previous 12 months. This figure is lower than most studies looking at clinically derived samples. Ballard and Walker (1999) systematically reviewed the literature and found a mean prevalence of delusions of 31% in all clinical settings and 23% in community settings, with Burns and colleagues (1990b) finding that delusions were three times more prevalent in men. Disease duration and age may be associated with an increased prevalence of neuropsychiatric symptoms, although this is by no means a consistent finding (Zhao et al., 2015).

Misidentification syndromes

Misidentification syndromes are sometimes called delusional misidentifications and might be better termed symptoms than syndromes. They are very common in AD, occurring in about 23–30% of patients at some time and in about 19% during a single year (Rubin et al., 1988; Burns et al., 1990c). They have been classified as delusions and as hallucinations depending on how the phenomena are understood. For example, the common assertion by patients with dementia that someone else has been in the house, when their family denies such a possibility, could be a paranoid delusional belief or a visual hallucination. In practice

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it is often not possible to clarify the experience well enough to determine the exact form of the psychotic experience.

Another common kind of misidentification is the conviction that a relative or friend is someone else (which may be a Capgras syndrome if the misidentified person is accepted as looking exactly the same as his or her 'double', though this may be difficult to tease out in AD). Commonly, a spouse is misidentified as a son or daughter, or vice versa, but sometimes the patient believes the misidentified person is a stranger and this may provoke a strong reaction. Other symptoms include beliefs that people or events on the television are actually in the living room and the misidentification of the patient's own image in the mirror as another person. Wrongly believing strangers to have been in the house appears to be the commonest form of misidentification, being found in 12–17% of patients at some point; misidentifying people occurs in about 12%; misidentifying images from the television is found in 6–12%; and misidentifying a mirror image occurs in about 4–7% (Rubin et al., 1988; Burns et al., 1990c). Overall, studies show that misidentification occurs in 30% of people with AD (Ballard and Walker, 1999). Like delusions, these misidentification syndromes appear to be more likely to occur in men (Burns et al., 1990c).

Hallucinations

Hallucinations are less common than delusions and misidentification syndromes. However, study figures here may be underestimates reflecting an unavoidable bias in the way in which the symptoms are rated. The scores are informant based and informants will probably be unaware of the full extent of someone else's internal hallucinatory experiences while it seems reasonable to believe that delusions and misidentifications are almost certain to reveal themselves. Visual hallucinations are more common than auditory hallucinations and while olfactory, gustatory, and tactile hallucinations also occur in AD, they are much rarer. Studies in clinical settings have found prevalence rates for all hallucinations of between 10% (Mega et al., 1996) and 40% (Gilley et al., 1997) in AD. In their systematic review, Ballard and Walker (1999) found mean prevalence rates of 21% for all hallucinations (14% for visual hallucinations and 7% for auditory hallucinations) in clinical settings. Hallucinations may be more common in younger patients (Burns et al., 1990d) but, as with delusions, studies have not demonstrated this consistently (Zhao et al., 2015).

Management of psychosis in AD

Pharmacological (Box 30.4) and nonpharmacological interventions may both be of benefit, although use of the former needs to be considered in light of their benefit versus potential risks (particularly in the case of antipsychotics).

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Nonpharmacologically, in addition to dealing with general health matters, treating the sensory deficits that may be exacerbating hallucinations, increasing the general level of stimulation, e.g. by arranging day care or attendance at a day centre, may be of benefit to someone who has hallucinations or misidentifications. Improved training to care providers to help their understanding of, and how to react to, people with dementia experiencing psychosis, aggression, and agitation is also important.

Mood changes

Alterations in mood are common in dementia, with depression being the most common. Here we are concerned with depression occurring during established AD; the relationship of depression to AD as a risk factor is considered in the section Risk factors for Alzheimer's disease and the concept of 'depressive pseudodementia' is dealt with in Chapter 39.

One problem is how we define the word 'depression'. Even separating studies looking at depressed mood, depressive symptoms, and depressive syndromes still leaves enormous variability, with rates varying from 0% to 87% for depressed mood (Knesevich et al., 1983; Merriam et al., 1988); from 0 to 89% for all depressive symptoms (Wragg and Jeste, 1989); and from 0% to 30% for depressive syndromes (Burns et al., 1990d; Teri and Wagner, 1991). These rates vary because different populations are sampled, different instruments are used, and different raters provide the rating. Problems in the assessment of depressive symptoms also occur because apathy can easily be mistaken for depression, while many depressive symptoms, e.g. poor appetite, weight loss, and sleep disturbance, are also common features of dementia itself. In addition, depressive symptoms in dementia tend to be associated more with psychotic symptoms and apathy, and less with negative cognitions such as hopelessness, suicidality, guilt, and low self-esteem (Olin et al., 2002; Rosenberg et al., 2005), and thus depression in dementia may represent a distinct syndrome with pathophysiological underpinnings that are different from the depression seen outside of dementia; this may have an impact on whether antidepressant medications are effective.

In a review of studies examining depressive syndromes diagnosed using standardized criteria, Ballard and colleagues (1996) found major depression to occur in 21% of dementia sufferers in clinical settings and 13% in the community. Depressive symptoms are also very common, with the Cache County Study reporting an initial prevalence of depressive symptoms of 29% at baseline (Steinberg et al., 2008). Over a five-year period, this study also noted that period prevalence for depression was very high at 77%. However, no clear association between depression and the severity of dementia has been found, with some studies showing depression to be more common in milder dementia and others showing the opposite. Depression decreases the quality of life of people with dementia, may reduce survival (Burns et al., 1991c), and so it would therefore appear to be important to treat it if possible.

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Early small trials of selective serotonin reuptake inhibitors (SSRIs) (Nyth et al., 1992; Lyketsos et al., 2003), moclobemide (Roth et al., 1996), and tricyclic antidepressants (TCAs) (Petracca et al., 1996) reported evidence of benefit for depression in dementia, but TCAs should be avoided because they worsen cognitive impairment and have higher drop-out rates (Taragano et al., 1997). However, the quality of most of these studies is poor and several others were negative (Dudas et al., 2018).

Reinforcing this evidence for lack of efficacy are the results from the United Kingdom (UK) Health Technology Assessment Study of the Use of Antidepressants for Depression in Dementia (HTA-SADD) (Banerjee et al., 2011); this double-blind, placebo-controlled trial in a large cohort of probable or possible AD patients with depression found no treatment benefit with either sertraline or mirtazapine and increased adverse events were noted in those on these medications. The lack of efficacy and potential increased side effects of sertraline have also been confirmed by the Phase II of the Depression in Alzheimer's Disease Study (DIADS-2) (Rosenberg et al., 2010; Weintraub et al., 2010), which compared sertraline 100mg with placebo in depression in AD and found no significant difference in symptom change or response or remission rates at either 12 (Rosenberg et al., 2010) or 24 weeks (Weintraub et al., 2010). They also reported an increase in adverse events on sertraline and concluded that the evidence does not support the use of SSRIs in depression in AD. These individual studies and others have been the subject of a recent Cochrane systematic review, which concluded that there was not strong support for the efficacy of antidepressants for depression in dementia and good evidence that they have little or no effect on improving scores on depression rating scales (Dudas et al., 2018).

These findings now leave clinicians with difficult choices in managing depression in dementia. However, as with trials of antipsychotics, subjects in these studies were less severely depressed than many encountered in clinical practice. Antidepressants may therefore retain a role in the treatment of more severe and prototypical depressive syndromes, although the argument that patients with more severe depression may differentially respond to antidepressants has not been supported (Drye et al., 2011). Though evidence supporting the use of antidepressants in AD is poor, it should be kept in mind that the evidence for antidepressant use to treat depression in other contexts which are associated with dementia is stronger, for example, in post stroke depression (Mead et al., 2012). Thus, antidepressant treatments may be of relevance in more 'pure' VaDs.

Simple social interventions, e.g. befriending or a day centre, should be considered and it is important to note that even in the pragmatic HTA-SADD trial, there appeared to be a natural amelioration in depressive symptoms with time in the placebo group (who had treatment as usual). Furthermore, other agents such as cholinesterase inhibitors may also be useful and electroconvulsive therapy (ECT) remains a treatment option

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for dementia patients, particularly for those with more severe depression, suicidality, or agitation/aggression. Although better studies are needed to clarify the safety of ECT and its efficacy, available case series are generally reassuring with regards to the use of ECT in people with dementia in terms of cognitive function (Rao and Lyketsos, 2000; Gauthier et al., 2010).

Elevation of mood in dementia is much less common and less frequently studied than depression. Burns and colleagues (1990d) found only one patient (out of 178) who reported manic symptoms and only six who had any observable evidence of mania. Similarly, point prevalence rates of euphoria and elation in the Cache County Study were less than 1% (Steinberg et al., 2008). Anxiety has been much less studied than even euphoria in dementia, but, consistent with clinical experience, it is a common symptom, with studies finding a rate ranging from 24% (Steinberg et al., 2008) to 50% (Patterson et al., 1990), and in the Cache County Study the five-year period prevalence of anxiety symptoms was 62% (Steinberg et al., 2008).

Behavioural symptoms

Apathy

Apathy is diminished motivation and manifests itself as a listlessness in which the patient has lost the drive to engage in goal-oriented behaviour and cognition (Starkstein and Leentjens, 2008). It is often confused with low mood and anhedonia, i.e. the loss of ability to enjoy previously pleasurable activities. Although they all may be present together, they are not the same phenomenon (Levy et al., 1998). The distinction is important because carers often think someone with AD is depressed when he/she has apathy as a part of the dementia. Apathy is probably the most common behavioural change in AD (Mega et al., 1996; Steinberg et al., 2008), although it is underdiagnosed. Apathy is common early in AD and it typically becomes more severe as the cognitive impairment worsens. At presentation, apathy is frequently a complaint given by relatives who often misunderstand it as laziness and become frustrated by it. Explaining that apathy is a feature of dementia can remove this misunderstanding and the tension it brings.

Previously apathy has been a somewhat neglected neuropsychiatric aspect of dementia, but more recently it has become a focus of academic and clinical interest. Although no formalized consensus criteria yet exist for apathy, a taskforce (Robert et al., 2009) has proposed that apathy be defined as 'a disorder of motivation that persists over time and meets the following requirements: i) the core feature of apathy, diminished motivation, must be present for at least four weeks; ii) two of the three dimensions of apathy (reduced goal-directed behaviour, goal-directed cognitive activity, and emotions) must also be present; iii) there should be

identifiable functional impairments attributable to the apathy; and iv) criteria are given to exclude symptoms and states that mimic apathy.'

Although there are no licensed pharmacological treatments available at the present time for apathy, a recent systematic review suggested that there is evidence that the cholinesterase inhibitors and memantine may be effective in treating this symptom, but there is less evidence for the efficacy of calcium antagonists and antipsychotics, and little or no evidence to support the use of antidepressants and anticonvulsants (Berman et al., 2012). Early small trials have reported positive results for stimulants such as methylphenidate, but the evidence is not robust enough for this treatment to enter mainstream clinical practice (Rosenberg et al., 2013). Nonpharmacological interventions such as exercise, multisensory stimuli, and pet therapy may also help, although rigorous data on their efficacy are lacking (Brodaty and Burns, 2012).

Overactivity and aberrant motor activity

Several overlapping phenomena involving overactive behaviour are commonly found in AD. The most well-known are agitation—which may be defined as painful inner tension associated with excessive motor activity (American Psychiatric Association, 1994) and often goes together with aggression (discussed in section Aggression and agitation)—and wandering. However, other 'aberrant motor behaviours' are recognized and sometimes measured, e.g. rummaging in drawers and repeatedly putting clothes on and then taking them off. Aberrant motor behaviour including wandering, purposeless hyperactivity, and rummaging appears to affect about a quarter of dementia patients (Gauthier et al., 2010). Other activities can include disrobing, intentional falling, hiding things, repetitive mannerisms, screaming/shouting, repetitive questioning, and making strange noises (Cohen-Mansfield et al., 1989)

The baseline rate for these behaviours in the Cache County Study was reported to be 7% and increased to nearly 30% after approximately five years, which is consistent with the notion that all such overactive behaviours tend to become more common with increasing severity of the dementia. As with other neuropsychiatric symptoms such as aggression and agitation, nonpharmacological environmental strategies may be helpful (see Chapter 19).

Aggression and agitation

Aggression and agitation are major problems in dementia. They occur commonly and can cause great distress to carers. They are a frequent reason for admission to hospital and transfer to residential care as well as leading to potentially faster cognitive and functional decline (Scarmeas et al., 2007). Aggression is open to different definitions and even when verbal aggression (shouting, swearing) is distinguished from physical aggression (punching, kicking, biting, pushing, pinching, etc.) there is still much scope for differences of opinion in each category about what

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constitutes aggression. Burns and colleagues (1990e) defined aggression narrowly as behaviour liable to cause physical injury to others and still found 20% of their AD subjects to have aggression. Broader definitions naturally lead to higher figures and verbal aggression is usually found to be two to three times more common than physical aggression. Burns and colleagues (1990e) also found aggression to be much more common in men with AD. They also found that it became more common with increasing cognitive impairment, rising from 8% in mild AD to 24% in severe AD. Agitation, which overlaps with motor overactivity, has rates in dementia that are similar to aggression, with point prevalence rates of 13–24% in the Cache County Study (Steinberg et al., 2008), although rates may be higher (29–60%) in clinical samples (Bergh and Selbæk, 2012).

Treatment of agitation and aggression is often similar to that used for psychosis (see Pharmacological treatment of aggression, agitation, and psychosis in AD and Box 30.4) and often treatment trials not unreasonably assess these problems together (e.g. psychosis may be causing aggressive behaviour). For those with experience of running mental health wards for admission of the most disturbed patients, it is striking how behaviours can often improve following admission with minimal pharmacological intervention, and this may serve to highlight the importance of the right environment and level of resource to properly manage very complex patients.

Neurovegetative symptoms

Sleep

Sleep disturbance is another common feature of dementia which can have devastating consequences for carers and is dealt with in more detail in Chapter 48. It may take the form of frequent waking, reduced sleep quality, or a disturbance to circadian rhythms. More recent studies have suggested an increased prevalence of sleep apnoea in AD, although studies have not consistently found this (Duthie et al., 2011).

The well-recognized pattern of day-night reversal was found to occur in 28% of patients in one study (Reisberg et al., 1987) and all forms of sleep disturbance have been found in 45–70% of AD patients (Rabins et al., 1982; Merriam et al., 1988). Sleep deprivation can eventually lead to exhaustion for the spouse if it persists, especially when it is associated with night wandering. To reduce the strain from sleep disturbance the spouse may sleep in another bed or in another room. Respite care can be of great help, although placement in residential care may finally be needed.

Pharmacologically, psychotropic drugs (hypnotics and antipsychotics) are frequently prescribed, although caution needs to be applied as these drugs are associated with significant adverse effects (Box 30.5), e.g. falls and over-sedation, and the evidence base for their efficacy is limited. The

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use of chronotropic agents, such as melatonin and bright light therapy have been investigated, with mixed results. A large well-conducted trial showed no beneficial effect of melatonin and this was confirmed by a recent Cochrane review that found no evidence to support the use of melatonin, but some evidence for the use of the sedative phenylpiperazine antidepressant trazodone, though this was based on a single small study (Singer et al., 2003, McCleery et al., 2016).

Box 30.5 Potential adverse effects of antipsychotics in dementia

- Worsening of cognitive function—equivalent to up to one year of cognitive decline
- Sedation and falls × 2 risk
- Extrapyrarnidal side effects
- Respiratory infections × 3 risk
- Prolonged QT_c and torsades de points × 2 risk
- Cerebrovascular event × 2 risk, although possibly × 9 risk in first week of antipsychotic use
- Mortality × 1.7–1.8 risk; may be higher with typical antipsychotics

Source: data from Kleijer, B. C. (2009). Risk of cerebrovascular events in elderly users of antipsychotics. *Journal of Psychopharmacology*, 23, 909–14.

Eating

Difficulties with feeding are common in dementia. These may progress from initial problems using cutlery with associated spillage of food through to complete dependence on others for feeding. In addition, there may be specific problem behaviours related to eating. Some patients refuse food, while others stuff food rapidly and clumsily into their mouths. The latter is common, occurring in 10% of people with AD (Burns et al., 1990e), and this figure is constant for all severities of dementia, although it is a more common feature of FTD and should raise this as a diagnostic option (see Chapter 33).

Sexual disinhibition

Sexual disinhibition is another problem that causes great distress to carers. It occurs in about 7% of people with dementia. It is rare in mild dementia and increases markedly with dementia severity (Burns et al., 1990e).

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Personality changes

Alterations in personality are ubiquitous in dementia and changes in personality are inseparable from some of the behavioural changes already discussed, e.g. apathy and sexual disinhibition. However, it is important to note that changes in personality do occur very early in AD and 75% of people with mild AD show such changes (Rubin et al., 1987). These may precede the cognitive deficits and are often subtle in form, but nonetheless they are frequently recognized and commented upon by carers. Such information should be cautiously interpreted, as family and friends are often too closely involved to be able to comment accurately and dispassionately and may either exaggerate or deny any changes. As AD progresses these initially subtle personality alterations tend to become more evident.

Personality changes not included in the section Behavioural changes are suspiciousness and disengagement. Suspiciousness is common and was found in 25% of AD subjects (Patterson and Bolger, 1994). It may or may not eventually consolidate into frank paranoid delusions and can cause great friction, as repeated accusations are made about the motives and behaviour of well-meaning carers and relatives. Disengagement refers to the detached state of emotional indifference seen often in AD and which is associated with a loss of rapport with other people. Patients are no longer concerned about the feelings of others or affected by their attention or lack of it. Such disengagement can be upsetting to relatives and may overlap with apathy, but it needs to be distinguished from the low mood of depression.

Physical symptoms

Neurological

Early in AD, neurological examination is usually normal. Focal neurological signs suggest a VaD or other cause of focal damage, while extrapyramidal signs may indicate DLB. Primitive reflexes, however, may occur early in AD, although their frequency increases as the dementia worsens. Burns and colleagues (1991a) found the snout reflex was easily the most common, occurring in 41% of their clinical sample. The grasp reflex was identified in 7% and the palmomental reflex in 2.5%. As the disease progresses, non-specific changes occur in both gait and balance, and myoclonic jerks and other seizures may develop. In the late stage, bilateral non-focal signs (e.g. upgoing plantars) may be seen.

Incontinence

Urinary incontinence is a common and well-recognized feature of AD and has been found in 48% of AD subjects (Burns et al., 1990a), though this figure disguises its strong association with disease severity. Incontinence was found in only 8% of those with mild AD but in 94% of patients with severe AD (Burns et al., 1990e). This association has important implications in diagnosis as incontinence early in a dementia is

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characteristic of other dementias, especially FTD and normal pressure hydrocephalus. Thus, the presence of urinary incontinence early in a dementia should lead to consideration of possible causes other than AD. It is also vital to consider and exclude other causes of incontinence, including urinary tract infections, especially in women or those with catheters, poor mobility, or failure to find the toilet in a strange environment (e.g. when someone has just been admitted to an inpatient unit).

General physical changes

AD is associated with a general physical deterioration in which the patient loses weight and develops a stooped posture associated with instability and gait abnormalities. AD patients are more prone to falls and this, combined with increased rates of osteoporosis, leads to enhanced likelihood of fractures compared to nondemented subjects (Duthie et al., 2011).

Weight loss may be an intrinsic feature of the disease process or secondary to progressive impairments, which can result in an inadequate consumption of food and fluids. Cronin-Stubbs and colleagues (1997) demonstrated that older people with AD lost weight at over three and a half times the rate of healthy age-matched controls, a rate of weight loss more severe than in older people with cancer. Weight loss was found to be more rapid in earlier stages of the disease and may occur prior to diagnosis, suggesting it is at least in part due to the disease process (LeBlanc et al., 2018). Whatever the cause, such marked weight loss is likely to contribute to the high mortality of AD.

Summary: Clinical features of Alzheimer's disease

While cognitive symptoms are central to the diagnosis of AD, neuropsychiatric and non-cognitive symptoms are arguably of more importance in management. Psychotic and mood symptoms are very common, a cause of distress to both patients and carers, and, in many cases, treatable in their own right. The behavioural disturbances, accompanying personality changes, and neurovegetative symptoms are also much more common than is usually recognized, can place great strain on carers, and their presence is a major risk factor for subsequent institutionalization.

Psychosocial interventions are usually necessary and should be the first consideration in treatment, though some of these (agitation, aggression, sleep disturbance, and psychosis) may respond to pharmacological treatment. The physical symptoms in AD remind us it is a debilitating condition requiring ongoing assessment and long-term palliative care.

Pharmacological treatment of aggression, agitation, and psychosis in AD

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Before explicitly considering drug treatment, it is worth reiterating that the initial effort should be in understanding and treating any underlying cause other than dementia driving the behaviour (e.g. pain or delirium). Given their low propensity for side effects, non-pharmacological treatments should be tried, ideally before drug treatment.

Antipsychotics

Several studies have evaluated whether drug treatments are effective for non-cognitive symptoms in dementia, but there is controversy about the risk-benefit ratio of these drugs in AD, and in dementia in general. Empirically, antipsychotics have been used to treat agitation, aggression, and psychosis in AD. However, the evidence base for their use in AD psychosis is less clear, as studies have tended to be small and have focused on agitation and general behavioural disturbance as outcomes. Several larger randomized trials of atypical antipsychotics in AD have been reported, e.g. the National Institute of Mental Health (NIMH) Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease (CATIE-AD) (Schneider et al., 2006b), and these, together with the smaller trials, have been subject to systematic review and meta-analysis (Sink et al., 2005; Ballard et al., 2006, 2011a; Schneider et al., 2006a). In summary, these reports suggest there is evidence for the efficacy, albeit of modest effect (effect size <0.5), for the use of certain antipsychotics (with the best evidence base being for risperidone, also the only drug to have a license for this indication in the UK) short term (fewer than 12 weeks) in the treatment of psychosis and aggression compared to placebo. The evidence for olanzapine is less clear, with contradictory findings reported, but there does appear to be a lack of benefit for quetiapine (Ballard et al., 2011a). However, many trials have tended to use very low, and therefore potentially suboptimal, doses of quetiapine. There is also little evidence that typical antipsychotics are efficacious for treating behavioural disturbance in dementia (although haloperidol may have some limited efficacy) and the evidence suggests increases in mortality are associated with these agents, too, at higher rates than for atypicals (see further later; see also Wang et al., 2005; Laredo et al., 2011) although rates of all-cause mortality seem to be similar across different atypicals (Farlow and Shamlan, 2017).

Evidence for the benefit of antipsychotics long term is also equivocal and withdrawal studies (e.g. the Dementia Antipsychotic Withdrawal Trial (DART-AD); see Ballard et al., 2009b) have failed to demonstrate worsening in neuropsychiatric symptoms after antipsychotic discontinuation, although many of the subjects in these studies were probably started on the drugs for milder degrees of symptoms; patients with higher baseline neuropsychiatric symptom scores may have higher relapse rates (Ballard et al., 2004). Most importantly, however, any benefit from antipsychotics in dementia needs to be weighed against the significant side effects associated with antipsychotic use (see Box 30.5), with numbers needed to treat about equal to the numbers needed to harm

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(Lancot et al., 1998), and in particular the increase in mortality in dementia patients taking these agents.

Regulatory bodies in different countries have issued warnings about an increased risk of death and cerebrovascular adverse events in people with dementia taking atypical antipsychotics, e.g. the Committee for the Safety of Medicines in the UK (2004) and the Food and Drug Administration (FDA) in the US (2005), with an extension of the warnings to include typical antipsychotics in 2007 by the FDA. These warnings have been based on a number of case control studies and case register data. Initially most of the data were not publicly available, and consequently in an early meta-analysis (Schneider et al., 2005) on the risk of death with atypical antipsychotics of 15 eligible trials, nine were unpublished with data extracted from abstracts presented at research meetings. This report noted a statistically significant increase of about 50% in mortality in patients taking atypical antipsychotics and a similar increase in those on haloperidol. Overall, there appears to be a 1.5- to 1.8-fold increase in mortality with antipsychotic use (Ballard et al., 2009b). This risk may be substantially higher in the first week of medication administration (Kleijer et al., 2009) and it appears to be sustained; the DART-AD study (Ballard et al., 2009b), a long-term randomized controlled trial (RCT) study in AD patients on antipsychotics, noted a significant excess of mortality over 24–54 months in people randomized to continue antipsychotic medication compared to those randomized to discontinue antipsychotic medication.

Comparisons with typical antipsychotics are difficult due to the lack of randomized evidence, but a retrospective cohort study of 22,890 older subjects taking typical and atypical antipsychotics found the former group to have a higher mortality (Wang et al., 2005). This finding is supported by a veteran/war widow cohort study (Hollis et al., 2007), which found that haloperidol was associated with an increased risk of death compared with individuals on olanzapine, although chlorpromazine had comparable levels of risk to atypicals. Another concern has been whether the use of antipsychotics hastens cognitive decline in dementia (McShane et al., 1997), and an analysis of the effect of atypical antipsychotic use (olanzapine, quetiapine, and risperidone) on cognitive function from the CATIE-AD trial (Vigen et al., 2011) found that AD patients who received an antipsychotic in the two weeks prior to cognitive testing had an average decline 2.46 points greater on Mini-Mental State Examination (MMSE) than placebo patients, although in this study it could not be determined whether this was a permanent and enduring effect on cognition or more related to the acute administration of these agents, e.g. enhancing sedation. The CATIE-AD study used an innovative endpoint of time to discontinuation as a proxy measure of the balance between efficacy and tolerability. Patients taking risperidone and olanzapine were less likely to discontinue medication due to lack of efficacy, but were more likely to discontinue due to side effects. The balance between these two aspects meant that the overall time to discontinuation was not

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significantly different between drug and placebo, again highlighting the close balance between benefit and harm for these medications.

Overall, it is clear that there are reasons for concern about the use of antipsychotics in dementia. They are associated with increased mortality and risk of cerebrovascular events, as well as possibly worsening cognition. There is also little doubt they have been overprescribed despite the modest benefits they appear to confer. For example, in the UK, it has previously been estimated that around 180,000 people with dementia are on antipsychotic medications in any one year, which equates to an additional 1,800 deaths and an additional 1,620 cerebrovascular adverse events (Banerjee, 2009). Increased understanding and awareness of this problem does seem to have caused a decline in total antipsychotic prescribing in this context, at least in the UK, mostly due to a decline in the use of first-generation drugs, and some evidence for positive changes in terms of lower rates of prescribing being temporally related to changes in guidelines and national warnings. (Stocks et al., 2017). It is worth noting, however, that patients entering the clinical trials were often much less psychotic and disturbed than many seen in clinical practice. Thus, in those with persistent and severe psychosis and associated agitation or aggression their use may be justified, especially given the even weaker evidence for alternative treatments (Thomas, 2011).

Antidepressants, mood stabilizers, and benzodiazepines

Trials using antidepressants to treat agitation have suggested that these agents may help. Two studies by Pollock (Pollock et al., 2002, 2007) examined the efficacy of citalopram. The later study compared citalopram with risperidone and found that both agents reduce agitation and psychotic symptoms to a comparable level. This conclusion has subsequently been supported by the CitAD study (Porsteinsson et al., 2014). This was a randomized controlled study of 186 patients with Alzheimer's disease and agitation, and showed that citalopram led to significant improvement in the primary endpoints of agitation and secondary endpoints of caregiver stress and total NPI with a number needed to treat of around seven. However, side effects included decreased cognition and increased QTc, albeit with no significant differences in serious adverse events or adherence between treatment and control groups. The dose used was 30mg (greater than the maximum recommended dose for the elderly in the UK). These data from this study have been further examined to suggest that the differences may be mediated by sedation, that the effect of citalopram treatment was not observed for the first three weeks of treatment, and that response was most likely in those with less severe dementia and agitation (Newell et al., 2016; Weintraub et al. 2015; Schneider et al., 2016). In addition, citalopram may also have benefits in remediating other psychiatric symptoms (Leonpacher et al., 2016).

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There have been a number of small studies examining the use of valproate for the treatment of agitation and aggression in AD. Baillon and colleagues (2018) noted that the benefits of valproic acid derivatives were equivocal and indeed were associated with significant adverse side effects. The evidence for divalproex sodium is no better; a large RCT (Tariot et al., 2011) confirmed the findings of previous RCTs in that divalproex sodium treatment had no effect on the emergence of agitation or psychosis (or slowing of cognitive impairment) and indeed was associated with significant toxic side effects. This is on top of a report of accelerated brain atrophy and cognitive impairment in patients with mild to moderate AD treated with divalproex sodium (Fleisher et al., 2011). As a result, sodium valproate cannot be recommended for use in the context of AD, a point made explicit in current UK NICE guidelines.

The potential benefit for carbamazepine remains unclear; two small reports have suggested benefit from carbamazepine in agitation and aggression (>300 mg/day) (Tariot et al., 1998; Olin et al., 2001), with effect sizes potentially greater than that seen with antipsychotics (Ballard et al., 2009a). Larger studies are needed, particularly as the potential toxicity of carbamazepine in AD may be an issue that limits the use of this agent. At time of writing, the efficacy of carbamazepine in the treatment of agitation was being examined in a UK-based clinical trial (SYMBAD study, <https://clinicaltrials.gov/ct2/show/NCT03031184>).

Benzodiazepines impair cognition (Tannenbaum et al., 2012) and may increase the risk of AD in themselves (Billioti de Gage et al., 2014). Data on their efficacy remain limited, and as such do not support the routine use of these agents for neuropsychiatric symptoms (Tampi and Tampi, 2014) though they may have some utility in emergency situations, where concern over the possibility of DLB diagnosis makes treatment with antipsychotics even less attractive.

Cholinesterase inhibitors

The fact that cholinesterase inhibitors improve cognition and function in AD is well established. However, their use in the treatment of aggression and agitation is less clear; any improvements have been noted in secondary analyses of datasets whose primary outcome was an improvement in cognition and/or function (Sink et al., 2005; Gauthier et al., 2010). Specific studies examining the effects of cholinesterase inhibitors on agitation or aggression have been disappointingly negative. For example, the UK multicentre, double-blind, placebo-controlled trial CALM-AD examined the efficacy of donepezil in treating agitation over a 12-week period, but it failed to find any significant improvement in its primary outcome measure of agitation (Howard et al., 2007).

Nevertheless, it is possible that there are potential benefits of cholinesterase inhibitors in ameliorating other neuropsychiatric domains in AD, e.g. apathy, excess motor activity (Gauthier et al., 2010), and possibly depression. In addition, judicious use of cholinesterase inhibitors

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early in the course of AD may delay or prevent the emergence of behavioural changes that occur with disease progression (Cummings et al., 2004).

Memantine

As with cholinesterase inhibitors, on the basis of post hoc analyses of previous RCTs, memantine has been suggested to have positive effects on agitation and aggression (Wilcock et al., 2008). Specific RCTs designed to investigate the impact of treatment with memantine on demented patients with agitation have failed to demonstrate benefit. For example, one large trial comparing memantine against placebo in AD patients with agitation found no improvements on the primary outcome measure (Cohen-Mansfield Agitation Inventory) albeit with some unspecified improvements on the neuropsychiatric inventory score (Fox et al., 2012). Other memantine trials have also been inconclusive (Schneider et al., 2011; Herrmann et al., 2013).

Newer potential treatments

Finding alternative and new agents for the treatment of agitation, aggression and psychosis as well as other neuropsychiatric symptoms in AD is topical at present. Examples include a phase-2, randomized, multicentre, double-blind, placebo-controlled trial of dextromethorphan hydrobromide–quinidine sulfate (a drug with complex actions including non-competitive NMDA antagonism, serotonin and norepinephrine reuptake inhibition, sigma 1 agonism, and nicotinic alpha3/beta4 antagonism) in AD found that this improved agitation and aggression with benefits seen in global measures and some carer measures and this agent appeared to be well tolerated (Cummings et al. 2015). Additionally, yokukansan—a Chinese herbal remedy featured in a meta-analysis of five RCTs—suggested small, but significant benefits on hallucinations, delusions, hallucinations, and agitation/aggression subscales on the neuropsychiatric inventory (Matsunaga et al., 2016).

A recent large double-blind RCT of Pimavanserin, a selective 5-HT_{2A} receptor inverse agonist and antagonist (approved in US for the treatment of Parkinson's disease psychosis), in nursing home patients with AD demonstrated a small- to medium-sized reduction in psychotic symptoms at six weeks in the treatment group, although the efficacy signal disappeared at 12 weeks (Ballard et al., 2018). Nevertheless, the drug was well tolerated and did not negatively affect cognition.

More robust evaluation of medications with anecdotal or only a limited evidence base in the treatment of agitation and aggression is also currently underway. For example, as mentioned, a large RCT is currently underway in the UK (the SYMBAD study) investigating carbamazepine and mirtazapine as treatment for agitation in dementia (<https://clinicaltrials.gov/ct2/show/NCT03031184>).

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Summary: Pharmacological treatments in AD

While helpful, such summaries of evidence hide many of the difficulties in interpreting studies and applying the evidence base to clinical practice. For example, atypical antipsychotic studies that were carried out in nursing homes often only included people with moderate to severe dementia (MMSE scores of less than 15), raising the issue of whether these findings can be generalized to less cognitively impaired and physically frail patients. Conversely, patients able to give consent to enter randomized studies tend to be less disturbed than many patients encountered in clinical practice. Finally, it is difficult to interpret what changes of a few points on rating scales mean in clinical practice.

As a general clinical approach, in patients with psychosis, agitation, or aggression, it is important to ask whether any agitation and aggression is being caused by undiagnosed or undertreated pain, constipation, hunger, or dehydration; indeed, the benefits of adequate analgesia for agitation in nursing home resident dementia patients have been highlighted in a recent cluster trial (Husebo et al., 2011). Environmental factors, caregiver interaction, and social stimulation (either too much or too little) also need to be considered.

Nonpharmacological approaches may be helpful, although the evidence for such interventions is often weak (Livingston et al., 2005) (see Chapter 19 for details). For example, the use of Melissa (lemon balm) aromatherapy has been advocated in treating agitation/aggression, although a recent rigorous double-blind study failed to show that aromatherapy was better than a cholinesterase inhibitor or placebo in treating agitation in AD patients (Burns et al., 2011). One systematic review identified person-centred care, dementia care mapping, and music and sensory therapy as being helpful in agitation (Livingston et al., 2014). A recent Cochrane review of music therapy concluded that there may be benefits in depression and overall behaviour but not specifically for aggression (Van der Steen et al., 2018).

If a nonpharmacological approach fails, then citalopram could be considered (Seitz et al., 2011), particularly if the agitation is mild or moderate. If the behavioural disturbance is more severe, treatment with an antipsychotic, specifically risperidone, should be considered. In view of the risks discussed in the section Antipsychotics, the clinician should explain his reasons for such treatment to patients and, if appropriate, their next of kin.

Risk factors for Alzheimer's disease

Identifying risk factors for AD is important for two main reasons. First, identification of risk factors and protective factors enables possible new treatments or public health interventions to be developed. Second, these aetiological factors may throw light on the pathogenesis of AD, stimulating new research that can further our understanding of the

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disease process, leading in turn to new treatment opportunities. Box 30.6 summarizes our present state of knowledge about the aetiological factors involved in AD.

Demographic risk factors

Age

It is easily forgotten that old age is the most important risk factor for AD, with AD's prevalence rising rapidly after 60, and approximately doubling every five years. But for how long does such a rise continue? It is still not clear whether the increase continues indefinitely (i.e. everyone would develop AD if they lived long enough). However, dementia is not always an inevitable consequence in the oldest old (Arosio et al., 2017).

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Box 30.6 Aetiological factors in Alzheimer's disease

Established risk factors

Age

Family history

Down's syndrome

Apolipoprotein E4 allele

Autosomal dominant mutations

Probable risk factors

Depression

Hypertension

Head injury

Possible risk factors

Female gender

Low intelligence/education

Diabetes

Smoking

Sensory deprivation

Possible protective factors

Apolipoprotein E2 allele

High intelligence/education

Consistent findings from studies in the oldest old are lacking, partly given the limited number of individuals that can be recruited from these age groups, challenges in developing appropriate cognitive measures in these populations given their often-significant sensory impairments and also problems in early studies with the use of appropriately operationalized diagnostic criteria. Early studies reported that the prevalence of dementia appeared to plateau for people in their 90s and may even drop in the very old (Fichter et al., 1995; Ritchie and Kildea, 1995) and indeed, in centenarians, if dementia does ensue, its onset is clinically delayed to an average of 92 years (Arosio et al. 2017). Incidence studies are a better measure of whether age itself is a causal factor in AD and dementia, and several studies (Matthews and Brayne, 2005) have countered the above findings, instead suggesting that dementia incidence continues to rise

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exponentially, with one US-based study reporting annual incidences of dementia of over 20% in 95-to 99-year-olds and greater than 40% in centenarians (Corrada et al., 2010). However, another prospective incidence study found that, while dementia incidence continues to increase beyond age 85, the rate of increase appears to slow relative to that of 65- to 85-year-olds (Hall et al., 2005). Overall, further work remains to be done to: i) clarify the role of ageing in dementia; ii) establish why there is a lack of an association between AD and apolipoprotein E (APOE, see Apolipoprotein E polymorphism) in the oldest old; and iii) explain the finding that up to half of the oldest old with dementia do not have obvious cerebral pathology to account for their cognitive deficits while some of those without clinical symptoms of dementia may carry significant pathological burden, for example, in terms of amyloid load. This suggests that the pathophysiological processes that dictate when an individual develops dementia, or more specifically AD, may vary considerably with age (Juva et al., 2000; Kawas and Corrada, 2006).

Sex

It is well recognized that AD is more common in women, but is female gender an independent risk factor? It could simply be that women live longer than men and consequently are at higher risk or live longer with the illness. As with studies examining age as a risk factor, sex differences in the incidence of AD have been reported in some but not all studies; one meta-analysis found women to have a higher incidence of AD than men but not a higher incidence of dementia in general (Gao et al., 1998). However, three more recent large longitudinal studies (Barnes et al., 2003; Corrada et al., 2010; Katz et al., 2012) found similar rates between men and women, even in the very old.

Nevertheless, others have reported that women have poorer cognitive outcomes than men (Laws et al., 2018). Such sex-related differences could be related to postmenopausal changes in oestrogens, genetic polymorphisms of sex-related genes, or an interaction of sex with APOE genotype (Gao et al., 1998). Of these possibilities most work has been done to investigate a possible role for sex hormones. Early systematic reviews and meta-analyses of cohort and case-control studies (Yaffe et al., 1998; LeBlanc et al., 2001; Nelson et al., 2002) reported oestrogen use to be associated with a reduction in the risk of developing AD of 29–34%. However, randomized trials, e.g. (Henderson et al., 2000; Mulnard et al., 2000; Wang et al., 2000) have failed to find any clinically meaningful evidence of benefit in treating patients with mild to moderate AD with oestrogen.

A large primary prevention trial, the Women's Health Initiative Memory Study (WHIMS), examined the possible benefit of HRT/ERT in reducing the frequency of, or time of, onset of dementia in postmenopausal women, but adverse outcomes led to both arms being terminated early (treatment led to increased rates of stroke, coronary heart disease, venous

thromboembolism, and breast carcinoma). The use of unopposed oestrogen over seven years was associated with a nonsignificant increased risk of dementia (hazard ratio (HR) = 1.49; 95% CI 0.83–2.66) (Shumaker et al., 2004), and treatment with combined oestrogen and progestin over four years led to a doubling of dementia risk (HR = 2.05; 95% CI 1.21–3.48) (Hays et al., 2003). Combining these two groups, there was a highly clinically and statistically significant increase in dementia in women taking HRT (HR = 1.76; 95% CI 1.19–2.60) (Shumaker et al., 2004).

However, it has been suggested that there may be a 'critical window' around the perimenopausal or early postmenopausal period, in other words, before significant Alzheimer's neuropathology has developed, during which oestrogen therapy may be beneficial in enhancing cognition, whereas later oestrogen treatment has negative effects. Support for this hypothesis was demonstrated in an observational cohort study (Whitmer et al., 2011) involving 1,524 women, which found that those who took hormone therapy at midlife had a 26% decreased risk of getting dementia compared to those who never took hormone therapy, whereas those taking hormone therapy only in late life had a 48% increased risk and women taking hormone therapy at both midlife and late life had a similar risk of dementia. However, as with similar studies of AD, risk factors confounded by indication (healthier, better-educated women with lower risk for dementia take HRT) might explain these findings.

Efforts have also been made to look at the potential protective effect of marriage. At least one systematic review has found that married people are less likely to develop dementia than lifelong single people or widows, though this finding may be confounded by differences in physical health and education and is not an effect of marriage per se (Sommerlad et al., 2018).

Ethnicity, race, country, and culture

It is estimated that the majority of people with dementia in the world live in developing countries (60% in 2001, rising to 71% by 2040 as a result of changing demographics; see Ferri et al., 2005). However, an outstanding issue is whether the inherent incidence of AD differs across the world and in different ethnic or racial groups.

A large number of studies have been published, although the findings have been contradictory and difficult to interpret. In a between country and race comparison Chandra and colleagues (2001) found a lower incidence of AD in older persons living in rural India (4.7/1000 person years) compared to a predominantly white population in the US (17.5/1000 person years). However, different social expectations of older people in the Indian cohort meant that individuals with cognitive decline may not have met functional impairment criteria for dementia, thus underestimating the true level of dementia in the Indian sample. A within-

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country comparison (Manhattan, US) of AD incidence between different racial groups by Tang and colleagues (2001) demonstrated that African-Americans had a greater risk for AD than white people (for 65- to 74-year-olds, incidence rate per person-year was 1.7% for African-Americans vs 0.4% for Caucasians and 4.4% vs 2.6%, respectively, for 75- to 84-year-olds), even adjusting for confounders such as education and vascular disease. However, the Cardiovascular Health Cohort (Fitzpatrick et al., 2004) only found marginal differences between African-Americans and white people, and these authors were cautious about the differences due to concerns about ascertainment methods applied during the data collection. A recent systematic review examining incidence and prevalence of dementia in the US among different racial and ethnic groups found higher prevalence rates among African-American and Caribbean-Hispanic populations, although there is large within population heterogeneity and use of current race/ethnicity classifications may be too crude to delineate specific race/ethnic risk factors (Mehta and Yeo, 2017).

Ethnicity, which encompasses shared culture, religion, language, geography, diet, and so on, may be a more powerful contributor to AD risk than race, given commonalities in life experience and environment between people of the same ethnic background; thus, epidemiological studies comparing different ethnicity despite similar race may give clues about risk or protective factors, and indeed provide an insight into the underlying pathophysiology of AD.

An important example was the Indianapolis-Ibadan Dementia Project which used identical assessment methods in Nigeria and Indianapolis, and reported an increased incidence of dementia and AD in African-Americans compared to Nigerians (Hendrie et al., 2001). One possible explanation for this finding was the observation that APOE ϵ 4 occurrence in the Nigerian cohort does not appear to be associated with increased AD risk (Gureje et al., 2006), suggesting that some protective mediating factor, potentially environmental, has a role in reducing risk in the Nigerian cohort. However, it should be noted that a more recent follow-up study from Nigeria reported a higher incidence rate of dementia than previously thought (Gureje et al., 2011) and thus the reported difference in the original study by Hendrie and colleagues (2001) may have related more to an underestimation of dementia incidence.

Overall, there remain significant problems with examining AD incidence across different races, cultures, ethnic groups, and countries, including problems with diagnostic classification, imprecise diagnostic instruments, imprecision in defining ethnic/racial groups, and different social expectations in certain cultures. In addition, even with better assessment and screening methodologies, the true prevalence and incidence of AD cannot be established without post-mortem confirmation of diagnosis. Until there are clear biological biomarkers for AD that can be easily applied in both high- and low-tech environments, we will remain

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uncertain as to the true variability in AD incidence across different racial, ethnic, and cultural groups.

Genetic risk factors

Family history

It has long been recognized that AD is more common in relatives of people with AD. Classic twin studies demonstrated a significantly higher concordance in monozygotic vs dizygotic twins (e.g. Pedersen et al., 2004). Meta-analysis suggests that those with a first-degree relative (parent, sibling, child) with AD have a 3.5-fold increase in their risk of developing AD (van Duijn et al., 1991). Generally, those with an early onset of the disease (before 65 years) show a stronger familial risk, although early-onset AD only accounts for 1–5% of all AD cases; conversely, the increased risk is very much reduced for those whose relatives develop AD in very old age. Nevertheless, the genetic contribution to AD is increasingly being revised upwards and new risk genes are continually being identified, with recent estimates suggesting a potential genetic contribution of up to 70% in AD (Pedersen et al., 2004; Gatz et al., 2005; Ballard et al., 2011b) (see Chapter 8 for a more detailed discussion of AD genetics).

Down's syndrome

Virtually all people with Down's syndrome have the neuropathological features of AD by the age of 40 years (Mann et al., 1986) and this is probably due to having an extra copy of the amyloid precursor protein gene located on chromosome 21. However, the prevalence of dementia in people with Down's is much less than 100%, even by age 50, although it is clearly markedly elevated for age (Zigman et al., 1996). The reason for this discrepancy between pathology and function (though it also mirrors some findings in the non-Down's syndrome elderly population) is not understood and complex interactions between maternal age and frequency of the APOE ϵ 4 allele (see next section) have been proposed. In addition, the added difficulties of making an accurate clinical diagnosis in this group are likely to contribute to the variable findings. Dementia in Down's syndrome is dealt with in detail in Chapter 47.

Autosomal dominant gene mutations

Three genetic loci have been identified with mutations conferring an autosomal dominant pattern of inheritance for AD with almost complete penetrance. These are mutations in the amyloid precursor protein gene on chromosome 21, in the presenilin 1 gene on chromosome 14, and in the presenilin 2 gene on chromosome 1. While all are associated with early-onset AD (before 65 years) they account for less than 2% of all AD cases (Farrer et al., 1997) and indeed do not seem to be present in even the majority of early-onset familial AD cases (Cruts et al., 1998). Their importance lies in the clues they may give about the pathogenesis of AD. For example, these mutations all lead to an excessive production of the

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pathogenetic long chain form of the amyloid beta protein (amyloid beta 42) (Hardy, 1997), and the presenilin 1 gene codes for an important enzyme (gamma secretase) involved in producing amyloid beta 42 protein (De Strooper et al., 1999; Saftig et al., 1999). More recently, a gene which had been identified as a potential risk gene in genome-wide association studies (GWAS) (sortilin related receptor 1, SORL1, involved in the endocytosis of low-density lipoprotein) has been identified as possibly having pathogenic variants resulting in an autosomal dominant pattern of inheritance (Pottier et al., 2012). Identification of families with deterministic mutations has also allowed the study of the development of the disease as members of these families can be identified and examined many years before an accurately predicted date of symptom onset. Studies of this sort have shed light on the length of time Alzheimer's pathology develops over and what the early changes might be. For example, such studies have demonstrated subtle cognitive, structural, and pathological changes many years (in some cases decades) prior to symptom onset (Bateman et al., 2012).

Genes that increase risk of Alzheimer's disease

There are many methods which can be employed to identify genes which increase the risk of a disease. These include linkage studies, candidate gene approaches, GWAS, meta-analyses of GWAS, pathway analysis, analysis of rare variants, approaches looking at changes in copy numbers, and whole genome analysis. These approaches have been applied to AD and in addition to the identification of autosomal dominant genes a number of other genes which increase the risk of AD have been identified. Whilst this wealth of data is welcome, it has resulted in a large number of genes being identified, some likely incorrectly, and some, where association does not necessarily relate to causation. This section focuses on those genes that have been identified and proven to be associated with AD in replication studies.

Apolipoprotein E (APOE) polymorphism

APOE is a plasma protein involved in lipid transport. The gene coding for APOE is located on chromosome 19 (19q13.2). It has three common alleles— $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ —which in the normal population have allele frequencies in white people of about 7%, 77%, and 16%, respectively (Zannis et al., 1993). Many studies have shown the $\epsilon 4$ allele to be much more common in AD subjects, occurring in 30–50% of patients (Roses, 1996). The estimated age-adjusted odds ratios for AD are 2.6 for $\epsilon 2/\epsilon 4$ heterozygotes, 3.2 for $\epsilon 3/\epsilon 4$, and 14.9 for $\epsilon 4/\epsilon 4$ homozygotes (Farrer et al., 1997). Thus, APOE $\epsilon 4$ alleles have a dose-dependent effect in increasing the risk for AD and notably there is a dose-dependent relationship between APOE $\epsilon 4$ expression and worse performance on episodic memory tasks in people with AD (Van der Vlies et al. 2007). Other studies have demonstrated that the increased risk conferred by APOE $\epsilon 4$ is related to it bringing forward the time of onset of AD (Roses, 1996). However, these striking findings need to be put in context. Up to

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50% of those who are homozygous for $\epsilon 4$ live to beyond 90 without developing AD and about two-thirds of those who develop AD have no $\epsilon 4$ allele (Henderson et al., 1995). It should also be noted that there is evidence the $\epsilon 2$ allele may be protective, as Farrer and colleagues (1997) found an odds ratio for AD of 0.6 for the combined $\epsilon 2/\epsilon 2$ and $\epsilon 2/\epsilon 3$ genotypes. Of all non-deterministic risk genes, APOE is by far the most robustly replicated and implicated in terms of risk of AD, and whilst it might account for a significant proportion of the heritability of AD, other genes are clearly contributory.

Other risk genes for Alzheimer's disease

The search for other risk genes using the techniques outlined earlier, including large GWAS meta-analysis of tens of thousands of cases and controls (Lambert et al., 2013), has been intensive and resulted in what is almost a surfeit of data: more than 500 genes have been suggested as potentially contributing to risk of AD. Discussion of all of these is beyond the scope of this chapter. Studies of this sort have been expanded to incorporate pathway analysis to identify commonly implicated biological processes including cholesterol metabolism and inflammation (Jones et al., 2010). This underlines the importance of studying the genetics of AD as this has allowed the development of novel patho-aetiological models, for example, galvanizing research focus on the role of inflammation and immunity as being important pathogenic processes in AD, and this is now translating in to new therapeutic strategies and ultimately trials (see Potential disease-modifying drugs for Alzheimer's disease).

Genes apart from APOE and SORL1 which are consistently implicated as risk genes for Alzheimer's disease include CLU (clusterin, a heat shock protein involved in apoptosis), PICALM (phosphatidylinositol binding clathrin assembly protein, involved in endocytosis), and TREM2 (triggering receptor expressed on myeloid cells 2, involved in white blood cell mediated immune response). Interest is also increasing in looking at 'resilience' genes, which reduce the risk of dementia, e.g. the A673T variant in amyloid precursor protein (APP) (Jonsson et al., 2012). These genetic findings are covered in greater detail in Chapter 8 and interested readers should consult the online meta-analysis website <http://www.alzgene.org> for up-to-date information.

Education, intelligence, mental activities, and cognitive reserve

Education, intelligence, and mental activities have all been mooted to modify the risk of incident AD. A common element uniting these factors is the notion of cognitive reserve, a hypothesis that compensatory processes or strategies, related to either brain function and structure (e.g. people with higher levels of education may have more synaptic connectivity and can therefore tolerate more neuronal loss before clinical deficits emerge) protect against the risk of dementia. Beyond this is the concept that mental engagement and activities, such as belonging to a social group, reading, and playing games, help build upon cognitive reserve and lessen

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the risk of dementia (this is discussed in more detail in Physical, cognitive, and social activity).

Valenzuela and Sachdev (2006) carried out a review of published data on the effects of premorbid IQ, education, occupation, and engagement in mental activities on incident dementia, and noted that the majority of studies indicated a protective effect of education (ten out of 15 studies), occupational attainment (nine out of 12), high premorbid IQ (two of two), and mental activities (six of six). Combining these as markers of cognitive reserve, Valenzuela and Sachdev (2006) suggested that individuals with high reserve had a decrease in AD risk of 46% compared to those with low reserve.

Individuals with higher cognitive reserve as measured by the proxies of education, occupational achievement, or engagement in leisure activities appeared to have a more rapid decline once the diagnosis of AD was made; this may be because people with greater cognitive reserve have higher levels of pathology at the 'point of inflection' where memory function begins to decline (for discussion, see Stern, 2009). In support of this, a functional neuroimaging study showed regional cerebral blood flow to be lower in better educated subjects in the parietal and temporal lobes compared with more poorly educated subjects who had been matched for the severity of their dementia, indicating they had more advanced disease (Stern et al., 1992).

What is not clear is how factors such as intelligence and education affect the risk of incident AD. Is it a case that these factors lead to more efficient use of brain networks and better synaptic transmission, the development of compensatory cognitive strategies, or allow one the ability to recruit alternative brain networks in the face of disease, and so the dementia presents later, or not at all if death supervenes?

Alternatively, do intelligence and education affect performance on objective cognitive tests so that people with poor education or lower intelligence fall below the threshold for dementia more easily and better educated/more intelligent people are better able to 'cover up' their deficits on testing?

There is evidence for the former; autopsy studies (Bennett et al., 2005; Roe et al., 2008) found that education (and brain volume) interacts with AD pathology to predict cognitive performance, and a longitudinal study (Roe et al., 2011) found that in individuals with normal cognitive function but high levels of CSF tau and phosphorylated tau at baseline (biomarkers for AD) the time to incident cognitive impairment was moderated by education and brain volume. Interestingly, one of the earlier religious orders studies which had followed a group of nuns for many years showed not only that those nuns with lower verbal ability in early life (a proxy measure of intelligence) had poorer cognitive functioning and a higher rate of AD, but also that at post-mortem all of those with neuropathological evidence of AD had low verbal ability (Snowdon et al., 1996). Therefore, higher intelligence may also possibly

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protect against the pathological process of AD itself. However, a biomarker study (Vemuri et al., 2011) observed that the association between cognition and the American National Adult Reading Test (a measure of premorbid IQ) was found to be additive rather than interactive with biomarkers of AD pathology. Clearly, further work is required to clarify the exact relationships between education, intelligence, cognitive reserve, and AD.

Depression as a possible risk factor for AD

It is generally agreed that in the early stages of the dementia process, people often seem to have symptoms of depression, and indeed their dementia may present initially with depression rather than overt cognitive changes. But is depression an independent risk factor for developing dementia or AD? Several case-control and cohort studies have examined this and a thorough meta-analysis (Ownby et al., 2006) identifying studies in which a specific diagnosis of depression (rather than depressive symptoms) found 20 good-quality published studies and reported that any history of depression doubled the risk of developing AD (odds ratios of 2.03 (95% CI: 1.73–2.38) for case-control studies and 1.90 (95% CI: 1.55–2.33) for cohort studies).

However, as there is often quite a short period between the episode of depression and the onset of dementia, it is not obvious whether the depression is an intrinsic feature of the dementia or a true risk factor for dementia. Nevertheless, a recent prospective study based on the Framingham cohort (Saczynski et al., 2010) found that depression was associated with double the risk of dementia and AD in older men and women over a 17-year follow-up period, supporting the hypothesis that depression is a risk factor for dementia, rather than the other way around.

It is not, however, clear how depression mediates its effect, although its associations with high cortisol levels, chronic inflammatory markers (e.g. tumour necrosis factor- α), and hypothalamic-pituitary-adrenal axis activation have been suggested as mediating processes. Depression may also have its effect via lifestyle factors; reduced physical activity and social engagement occur in depression and these are both factors associated with an increased risk of dementia. Alternatively, increased vascular pathology associated with depression (Thomas et al., 2004) could provide the missing link, as vascular factors are associated with increased AD. Against this argument is the finding from the Framingham study (Saczynski et al., 2010) that even controlling for major vascular risk factors did not alter the AD risk level associated with depression.

Vascular risk factors

Over recent years the debate about the relationship of AD to VaD has been complicated or clarified (depending on your view) by evidence that vascular disease may directly contribute to the pathology of AD. The so-called angiogenesis hypothesis proposes that elevated blood pressure

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leads to small vessel damage and inflammation with secondary increases in amyloid and neural loss (Kuller and Lopez, 2011). In fact, this is far from a new idea, as in his original paper Alois Alzheimer (1907) described vascular pathology at post-mortem in Auguste D. This finding has been confirmed by more recent pathological data showing that AD patients have a high level of white matter lesions and small grey matter infarcts. Both APOE and homocysteine (discussed in Homocysteine, vitamin B₁₂, and folate) are also vascular risk factors and may exert their pathogenic effects in AD via vascular disease. It has been proposed that a history of hypertension, as long as ten and 15 years before the onset of dementia, increases the rate of AD (Skoog et al., 1996), and therefore that treatment of systolic hypertension in older people might reduce the rate of dementia and AD (Forette et al., 1998). However, a review of longitudinal studies (Daviglus et al., 2011) failed to find any significant difference in the incidence of AD between subjects with and without hypertension, and pooled analyses examining the treatment effect of antihypertensives on the incidence of AD have also found no statistically significant effect (RR: 0.90, 95% CI: 0.79–1.03) (Guan et al., 2011). Specific trials of antihypertensives in established disease, even those with multiple putative disease modifying mechanisms, have been negative (Lawlor et al. 2018).

Unfortunately, research into the potential risk reduction effects of antihypertensives is hampered by the fact that studies have focused on older individuals and therefore may have 'missed the boat' in terms of preventing any vascular changes and thus consequent amyloid formation. These studies also have several other problems, including: i) inconsistent diagnostic criteria for dementia; ii) different definitions of hypertension; iii) focusing on vascular endpoints rather than on dementia; and iv) probable bias due to survivor effects, i.e. patients who would normally have died with cerebrovascular disease but remained alive because of successful control of their hypertension may be the people with the highest levels of vascular damage (therefore the highest risk of AD according to the angiogenesis hypothesis), thereby actually increasing the overall incidence of AD (Kuller and Lopez, 2011).

Therefore, the benefits of blood pressure reduction on dementia risk remain unclear at the current time. Even considering the treatment of hypertension earlier on in midlife may not be helpful for reducing AD. The Uppsala Longitudinal Study of Adult Men, which started in 1970 when subjects were 50 years old and has followed subjects for up to 40 years, failed to find any association between vascular risk factors and AD incidence (Rönnemaa et al., 2011). However, high systolic blood pressure did appear to be a risk factor for all types of dementia, in particular VaD and mixed dementia, so antihypertensive treatment may be more beneficial for these dementias than for AD.

Beyond hypertension, other manifestations of vascular disease, including ischaemic heart disease, heart failure, renal failure, atrial fibrillation, and previous cerebrovascular disease, are associated with an increased risk of

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dementia of all types including AD (Bunch et al., 2010; Dublin et al., 2011).

Elevated total cholesterol in midlife, an established risk factor for coronary heart disease and stroke disease, has been associated with an increased risk of developing dementia in cohort studies (Kivipelto et al., 2001; Whitmer et al., 2005), although there is a lack of association between high cholesterol in late life and AD (Anstey et al., 2008). Reduction of cholesterol using statins has been proposed to modify AD through several mechanisms, in addition to the headline effect of cholesterol lowering, including antioxidative effects, inhibition of butyrylcholinesterase, and increasing the trafficking of amyloid precursor protein (Darvesh et al., 2004). Two cross-sectional analyses have reported a reduction in dementia in people taking statins (Jick et al., 2000; Wolozin et al., 2000). However, concern was expressed about 'bias by indication' in these studies (i.e. healthier, better educated people are more likely to take statins), and this view is supported by the finding in a five-year prospective study that, while on cross-sectional analysis, statin use was inversely associated with dementia, statins did not reduce incident dementia risk (Zandi et al., 2005). Further caution about the potential benefits of statins in reducing AD and dementia arises from the findings in two large randomized placebo-controlled trials of two different statins—simvastatin in the Heart Protection Study (Heart Protection Study Collaborative, 2002) and pravastatin in the PROSPER study (Shepherd et al., 2002)—which both failed to find any benefits of statins on cognitive function or in reducing dementia risk.

Other vascular risk factors that may increase the risk of AD are the metabolic factors obesity and diabetes. Diabetes doubles the risk of VaD and, more specifically, AD (Ahtiluoto et al., 2010), with the risk increased in APOE ϵ 4 carriers. A systematic review by Biessels and colleagues (2006) noted that a majority of cohort studies have suggested that diabetes is associated with an increased risk of incident AD, although limitations in studies such as different diagnostic criteria for diabetes, lack of information on duration of the diabetes, and the quality of glycaemic control make it difficult to determine what elements of diabetes contribute to increasing the risk of AD.

Obesity in midlife is linked with an increased incidence of AD with risks in the order of 2–5 times in individuals with body mass indexes (BMI) more than 30 (Gustafson, 2008; Fitzpatrick et al., 2009); increased waist-to-hip ratios may also be a specific risk factor (Gustafson et al., 2009). However, obesity is often co-associated with vascular and metabolic disturbances (e.g. hypercholesterolaemia, hyperglycaemia, hypertension, hypertriglyceridaemia, and reduced levels of high-density lipoprotein, i.e. the 'metabolic' syndrome), which in themselves have been associated with AD risk, making it difficult to disentangle the unique contribution of obesity to AD risk. Indeed, these vascular/metabolic risk factors may be additive in their effects. For example, in one study, combining obesity with hypertension and high cholesterol led to a much larger combined

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risk (OR 6.2) (Kivipelto et al., 2005), and in another prospective study (over 5.5 years) diabetes, smoking, hypertension, and heart disease all increased the risk of AD, but their combinative effect was much stronger, increasing the risk by over threefold (Luchsinger et al., 2005).

This section raises the attractive possibility that lifestyle modification might decrease the risk of Alzheimer's disease. Studies have been completed to identify the impact of single lifestyle interventions but have had disappointing results. More recently multi-interventional studies have been reported, which have again been largely disappointing, though the FINGER study did show benefits in cognition for those at high risk assigned to multiple intervention addressing diet, exercise, cognitive training, and vascular risk (Ngandu et al., 2015).

Head injury

A meta-analysis of 15 case-control studies of head injury (with loss of consciousness) showed it to be associated with an increased risk of AD (OR 1.58, 95% CI 1.21–2.06) (Fleminger et al., 2003) and this risk appears to be specific to men. However, one major criticism is that early studies used retrospective assessments from relatives, raising the risk of recollection bias. Interestingly, however, a study using a prospective historical cohort design of Second World War veterans who had documented nonpenetrating head injuries demonstrated that both moderate and severe head injury were associated with a significant risk of AD (Plassman et al., 2000).

Further evidence for head injury effects on AD risk come from pathology in that head injury leads to a disturbed balance between amyloid beta genesis and catabolism, leading to an increase in amyloid beta deposits. Indeed, amyloid deposition has been reported to occur within hours of the injury (Johnson et al., 2010). The potential increased risk following repeated minor head injury has become a topic of interest in the UK following the suggestion that there is an increased risk of dementia in football players who have repeatedly headed a heavy football. This has led to funding to investigate this possible link in footballers and the results of these studies are awaited. In the US there are concerns around the safety of American football (see Mez et al., 2017) with evidence of players having traumatic encephalopathy. Whether this means it causes an excess of dementia, and whether it associates with AD, are separate entities.

Sensory deprivation

Case control studies, systematic reviews, and meta-analyses have been consistent in identifying hearing loss as a risk factor for dementia, though whether it is a specific risk factor for AD is less clear (Livingston et al., 2017; Loughrey et al., 2018). The interest in this is enhanced by the fact that this risk factor may be modifiable by correcting hearing difficulties, though we do not yet know whether such intervention is beneficial. The role of visual impairment is not as well studied, but results from the

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recent ProVIDe study in the UK found a high incidence of visual impairment among those with dementia, much of which could be corrected by providing the right prescription spectacles (Bowen et al., 2016). This highlights the importance of not overlooking what may seem to be simple interventions (for example, getting the right spectacles) but which might make rapid and significant improvements to quality of life.

Other possible risk factors

Metals

Studies some years ago showed increased aluminium in the brains of subjects with AD and suggested that aluminium is neurotoxic (Crapper et al., 1973; Trapp et al., 1978). This led to the suggestion that it may play a role in the causation of AD, supported by some epidemiological evidence of higher rates of AD in areas with high aluminium content in the drinking water (Doll, 1993). However, other studies have not confirmed these early findings and it is clear aluminium is neither necessary nor sufficient to cause AD (Walton, 1991).

More recently, attention has switched to other metals including iron, zinc, and copper, whose levels in the brain appear to be raised and whose homeostasis is disordered in AD. This has led to the hypothesis that these metals may increase oxidative damage and the formation of amyloid beta plaques (Maynard et al., 2005). However, the role of metallobiology in the pathogenesis of AD is far from resolved, as research findings are often controversial and contradictory (Schrag et al., 2011).

Smoking

It has been hypothesized that smoking increases nicotinic receptors in the cortex and this could counteract the cholinergic deficit in AD, and smoking has been firmly identified as a protective factor in Parkinson's disease (Gigante et al., 2017). The role of nicotine as a potential neuroprotective agent in AD has received support from the finding that nicotine treatment reduces beta-amyloid deposition in mice (Hellstrom-Lindahl et al., 2004). In addition, early case-control studies suggested that smokers had a 20% reduction in AD (Graves et al., 1991). However, a meta-analysis of 19 prospective studies (Anstey et al., 2007) with at least 12 months of follow-up has refuted the argument that smoking may be protective for AD: current smokers had an incident risk of 1.79 (95% CI: 1.43, 2.23) for developing AD (with a comparable level of risk for incident VaD) compared to non-smokers. Incidence risks were similar when comparing current vs former smokers (pooled RR = 1.70; 95% CI, 1.25–2.31). But the view that nicotine may be neuroprotective has received support from randomized trials reporting benefits of nicotine therapy on cognition (e.g. Newhouse et al., 2012), although whether it reduces the development of AD or dementia remains to be demonstrated.

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Homocysteine, vitamin B₁₂, and folate

Cognitive impairment is associated with deficiencies in folate and vitamin B₁₂. Homocysteine is an amino acid intermediary in methionine metabolism and its blood levels increase with deficiencies in folate and B₁₂ because its elimination is dependent on these vitamins, and the risk of cognitive impairment and dementia associated with their deficiencies may be related to raised homocysteine levels.

High homocysteine levels appear to occur in AD compared to healthy older people, although a meta-analysis of prospective data has not provided conclusive evidence that homocysteine enhances the risk of developing AD (Ho et al., 2011). In addition, systematic reviews of intervention studies have found no evidence for any benefit on cognition or dementia using B₁₂ with and without folate even when associated with a lowering of homocysteine or for B vitamin supplementation more broadly (Malouf and Grimley Evans, 2009; Ford and Almeida, 2012; McCleery et al., 2018).

Frailty and weight loss

Reduced muscle strength and general frailty have been associated with an increased risk of dementia, and while midlife obesity with high BMI is associated with dementia risk, this situation reverses in old age, with low BMI being associated with incident AD (Fitzpatrick et al., 2009); however, it is possible that these factors are actually markers of dementia pathology rather than being causative, and thus are not true risk factors.

Alcohol

Previous meta-analyses of alcohol use have suggested there may be a 'U-shaped' relationship between alcohol consumption and dementia risk (Anstey et al., 2009; Weuve et al., 2012). Higher levels of alcohol intake are likely to increase the risk of dementia, possibly through well-established neurotoxic pathways such as Wernicke-Korsakoff syndrome, which may be underdiagnosed in heavy drinkers as well as direct neurotoxic effects leading to particularly cerebellar and frontal cortex deficits. It has been asserted that individuals who drink mild to moderate amounts of alcohol have a lower risk of AD and all types of dementia. Part of this effect is thought to be mediated through the indirect effect on cardiovascular health or as part of antioxidant process (e.g. high levels of antioxidants are present in red wine), although the exact neurobiological underpinnings are not known. More recently, however, the protective effects of moderate drinking on the brain has been questioned (e.g. Topiwala et al., 2017) in that non-drinking groups may contain a lot of people who have physical ill-health and their lack of alcohol consumption may be related to this. Thus, the relationship may be more 'J-shaped'.

Protective factors

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Anti-inflammatory medication

A review of case-control studies has suggested arthritis, nonsteroidal anti-inflammatory drugs, and steroids to be protective factors for AD, reducing the risk by about 50% (McGeer et al., 1996). This fits with current views that AD is associated with an inflammatory response in the brain because senile plaques are associated with prominent astrogliosis and microglial activation (Dickson et al., 1988) and pro-inflammatory cytokines are increased in the brain in AD subjects (Wood et al., 1993), as well as the association for genes involved in inflammatory pathways with AD. A dampener for enthusiasm about the role of inflammation in AD is that all RCTs using anti-inflammatory drugs, including ibuprofen, prednisolone, naproxen, and COX inhibitors, in established AD have been negative (Aisen et al., 2000; Aisen et al., 2003; Imbimbo, 2004; Reines et al., 2004; Lyketsos et al., 2007).

Vitamins, antioxidants, and nutritional supplements

Oxidative stress is thought to be important in the development of dementia and neurons are especially vulnerable to oxidative stress because the brain has a high oxygen consumption and a lack of antioxidant enzymes, e.g. superoxide dismutase (SOD-1), compared with other organs (Esposito et al., 2002), and is more dependent on dietary antioxidants, including tocopherols, ascorbic acid, carotenoids, vitamin A, and flavonoids. Although using vitamins as antioxidants has been frequently claimed to be protective against AD, cross-sectional and cohort studies have reported mixed findings on the possibility of nutritional and/or supplementary dietary antioxidants reducing the risk of dementia (Engelhart et al., 2002; Morris et al., 2002; Tabet et al., 2002; Larrieu et al., 2004; Engelhart et al., 2005). It is possible the characterization of oxidative stress as an exclusively negative cellular event may be simplistic. Reactive oxygen species may have physiological cellular roles to play, for example, as signalling molecules, including the induction of pathways protective against neurodegeneration (Underwood et al., 2010).

A randomized trial of vitamin E supplementation in AD involving moderately impaired subjects reported that after adjustment for baseline MMSE (but not before), vitamin E delayed time to a composite endpoint by 230 days (Sano et al., 1997). However, there were no differences in a range of secondary outcome measures including ADAS-Cog and MMSE. Another randomized trial of 769 subjects compared progression to possible or probable AD in subjects with amnesic MCI (Petersen et al., 2005). Subjects were randomized to vitamin E (2000 IU), donepezil (10mg), or placebo for three years and no difference in outcome was observed, casting doubt on the benefits of antioxidant treatment in preventing or slowing the development of AD. Similarly, a large RCT of 6,377 older women on 600 IU of vitamin E on alternate days (Kang et al., 2006) found no difference between treatment and control groups on measures of cognitive function after 5.6 years and 9.6 years of treatment.

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In summary, there is no good evidence to support vitamin E supplementation to either treat or prevent AD.

Omega-3 fatty acids, frequently obtained from fish oils, have been similarly mooted to have a range of health benefits mediated by their modulatory effects on inflammatory pathways. However, their potential effect on the incidence of AD has not been conclusively established (for discussion, see Daviglus et al., 2011).

General dietary changes may, however, offer some benefits in reducing the risk of AD. Emerging evidence has suggested that medium-to-high fruit and vegetable intake or adherence to a Mediterranean diet may reduce the risk of AD occurrence (Daviglus et al., 2011) and this is generally supported in systematic review, although caution needs to be applied to the findings of these dietary studies as individuals who take additional nutritional supplements and/or eat healthily also tend to be better educated and more physically fit (see Physical, cognitive, and social activity).

Once a risk factor has been identified, a sensible idea is to try to correct that risk factor in a hope of preventing disease or slowing decline once disease is established. One nutritional supplement which is now commercially available is Fortasyn Connect (also known as Souvenaid), a mixture of nutrients designed to maximize neuronal and synaptic function. RCTs have suggested benefit on cognitive tests in those with mild AD, though no benefit was seen in the primary outcome for those with MCI (Soininen et al., 2017).

Physical, cognitive, and social activity

The cardiovascular benefits of physical activity are well established and, given the putative linkage between vascular risk factors and AD as well as evidence in transgenic animal studies that physical activity reduces AD pathology, it is not unreasonable to hypothesize that physical activity may reduce AD risk. A meta-analysis of nine cohort studies (Daviglus et al., 2011) found that higher levels of physical activity were associated with lower risk of incident AD (HR = 0.72; 95% CI, 0.53–0.98). However, such studies often relied on self-reports of physical activity rather than objective measures, associations were not always statistically significant, and in some studies physical activity appeared to increase the risk of AD (Daviglus et al., 2011). Nevertheless, a subsequent Australian prospective study of older individuals (50+ years) randomly allocated to an education and usual care group or to a 24-week home-based programme of physical activity demonstrated sustained benefits of the exercise intervention up to 18 months, in terms of improvements in global cognition and delayed recall (Lautenschlager et al., 2008). Sadly, this benefit has not been replicated in further good-quality RCTs and methodological differences make meta-analysis challenging (Du et al., 2018).

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Cognitive engagement and leisure activity involvement may also have protective effects, perhaps by improving cognitive reserve, although the evidence base is still limited. Studies in this area suffer from the inevitable inclusion of individuals who tend to be better educated and healthier, factors (as already discussed) that in themselves reduce AD risk. Furthermore, it may be that in individuals with prodromal AD, the direct effects of the disease cause early social disengagement and reduced motivation and drive, which may accentuate the apparent 'difference' between healthy individuals who are socially and cognitively active compared to those who go on to develop AD.

Recent large epidemiological studies have examined the incidence of dementia in both the US and UK and have found fewer cases than expected. Retrospective analyses to identify the potential reasons for this are difficult, but both improvement in vascular health and education have been suggested, with the decline in expected cases in the Framingham study being seen only in those with high school diploma education or better (Satizabal et al., 2016, Matthews et al., 2016). Whether increasing social mental activity can bring benefit after the condition is manifest is even less clear, though there is some early evidence that social events such as 'singing for the brain' or computerized 'brain training' may help, whereas conversely loneliness may increase risk of dementia (Savulich et al., 2017; Osman et al., 2016, Rafinsson et al., 2017). Further work is required to understand better both the positive and negative impacts of social, physical, and environmental factors; challenges to this include the necessity to look at these lifestyle factors well before the emergence of dementia. Studies such as the UK PREVENT study are taking this long view perspective (<http://www.preventdementia.co.uk>).

Prognosis of Alzheimer's disease

The natural history of Alzheimer's disease

Every old age psychiatrist is familiar with the considerable variability in the pattern and progress of AD. All the studies following the natural history of the disease bear this out as they show substantial variations in symptomatology and rates of decline. The practical consequence of this for the clinician is that it is very difficult to give accurate predictions to patients or their families about the likely progress of the disease after the diagnosis has been made. However, despite these uncertainties, patients and relatives will continue to seek information on prognosis, and two of the most common outcomes of interest are time to institutionalization into residential or nursing home care, and time to death.

Institutionalization

Data compiled by the National Alzheimer Coordinating Centre (Spackman et al., 2011) have suggested annual probabilities of institutionalization of 1.2, 3.4, and 6.6% for mild, moderate, and severe AD dementia, respectively. A higher overall annual incidence of 11.84% was observed in a two-year prospective French study (REAL-FR (Gillette-Guyonnet et al.,

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2011)), thus highlighting the wide range of progression evident even in reasonably powered studies. Established predictors of institutionalization include the presence of behavioural symptoms, severe impairments in ADLs and cognition, having a paid (versus family) carer, living alone, and depression (Knopman et al., 1988, Habermann et al., 2009). Caregiver factors also probably have a significant role in predicting early nursing home placement. For example, a prospective study (Gaugler et al., 2003) identified that older age of carers (more than 80 years) and high perception of care burden by the carers themselves predicted higher early institutionalization. This study and other evidence show that there is a complex interaction between patient and caregiver factors that influences the course of the pathway to nursing care. This underlines the fact that it is always important to consider the needs of caregivers in the assessment of management of patients with dementia (Gaugler et al., 2011).

Death

Time from diagnosis to death is highly variable, with the length of survival from diagnosis ranging from one year up to 20 years. This is highly dependent on how early the diagnosis is made, although certain other factors, e.g. age at onset and comorbidity are also important. The median life-expectancy after diagnosis appears to be about five to ten years for patients diagnosed with AD in their 60s and 70s (equivalent to approximately 70% reduction in expected median lifespan) but only between three to four years if patients are in their 90s (an approximate 40% reduction in expected median lifespan) (Xie et al., 2008; Zanetti et al., 2009). Unsurprisingly, the mildest patients at outset tend to show the longest times to both institutionalization and death. A recent large naturalistic UK-based study arrived at a mean time of survival of around seven years from diagnosis to death (Price et al., 2017).

The cause of death in AD can be difficult to determine. As with other chronic diseases in older people, many people will die *with* the disease rather than *from* it. A Swedish autopsy study based on data from 1974–2004 found that the most common cause of death in AD patients was bronchopneumonia (47.3%) (Brunnstrom and Englund, 2009). Difficulties in the terminal stages with feeding and poor airway protection may be contributory. Since AD is associated with marked weight loss and physical decline (Cronin-Stubbs et al., 1997), these are likely to contribute in their own right to death in many people with advanced disease, although frequently AD may not be mentioned on the death certificate (Burns et al., 1990a).

Whether AD directly causes death is less certain, although it seems plausible as some patients do simply fade away without any other obvious cause for death occurring. Many others develop other complications of immobility and physical debilitation and die of a combination of causes.

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Measuring rates of decline

Two kinds of instrument (global rating scales and cognitive scales) have been used to try to measure the rate of decline in AD. Global measures, e.g. the Clinical Dementia Rating Scale (CDR) (Hughes et al., 1982), tend to change very slowly over a few years and so are not useful measures of change clinically. Cognitive scales can show significant changes over the course of a year. Some of these are in common use and familiarity with the data derived from research may help a clinician to see how rapidly any patient is declining compared with these norms and therefore aid the prediction of progress and outcome, although the substantial variability should always be borne in mind. The annual rate of change in the MMSE (Folstein et al., 1975) is about 2.5 points a year for moderately affected patients, with higher rates for more severely affected patients and lower rates for milder cases (Salmon et al., 1990). The REAL-FR study (Cortes et al., 2008) noted that after two years 11% of patients lost more than nine points on the MMSE, 66% lost between three and nine points, but a substantial minority (23%) remained stable or improved, highlighting the heterogeneity in cognitive decline among AD patients as well as evidence of plateauing.

Two more comprehensive instruments are the CAMCOG (the cognitive component of the Cambridge Mental Disorders of the Elderly (CAMDEX)) and the ADAS-Cog (the Alzheimer's Disease Assessment Scale—cognitive subscale). Burns et al. (1991b) used the CAMCOG to follow the progress of 110 AD patients. They found a drop of about 12 points in the first year (maximum score 107 with 80/79 as the cut-off for dementia). This included change in every main subsection, but many of the scores were already near the floor at baseline and this instrument appears less useful in more advanced dementia. Older studies have used the ADAS-Cog (maximum score 70, higher scores = worse performance) and have shown an annual rate of increase of between eight and nine points (Kramer-Ginsberg et al., 1988; Yesavage et al., 1988). A more recent finding from the REAL-FR study reported a slower rate of progression of an average of a 4.5 point gain per year on the ADAS-Cog over a four-year period (Gillette-Guyonnet et al., 2011), which may reflect changes in management of AD (memory clinics and availability of symptomatic drugs) over the past 15–20 years.

Predicting rates of decline

Within the rough framework of the above figures for rates of decline and time to institutionalization and death, are there any clinical features that can help sharpen the prediction in individual cases? Certainly, the more severe the dementia the more rapid is the rate of decline (Morris et al., 1993). Consistent with this, the decline is nonlinear, being slower at the milder stage but accelerating as the dementia progresses (Teri et al., 1995).

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In some studies, the level of education has been demonstrated to be a predictor of decline (see discussion in Physical, cognitive, and social activity).

Extrapyramidal symptoms appear to predict more rapid deterioration in AD (Lopez et al., 1997), although results are complicated by the likely admixture in earlier studies of patients with AD and DLB and that the prognosis of DLB is significantly poorer in studies that directly compare the two conditions (Miller et al., 1991, Price et al., 2017). Gait apraxia may also be a marker of poor survival (Paradise et al., 2009), although whether gait apraxia is a reflection of or due to more severe brain disease, and thus shorter survival, or that it leads to survival-shortening falls or immobility is not clear. Several studies have found psychotic symptoms to predict more rapid deterioration, although when groups have been matched for severity of AD at outset the findings have been mixed. Some studies have found that psychosis does still predict rate of decline (Chui et al., 1994; Stern et al., 1994), but not all (Reisberg et al., 1986; Chen et al., 1991). One longitudinal study has not found depression to predict decline (Lopez et al., 1990), but, unsurprisingly, it has been shown to be associated with greater impairment on ADLs (Pearson et al., 1989).

Other factors that have been investigated without a clear conclusion include sex, age of onset, APOE genotype, and concomitant cerebrovascular disease. Data (see previous sections) on oestrogen replacement, lipid-lowering agents, vitamins (B₆, B₁₂, E), omega-3 fatty acid supplementation, and NSAIDs have not indicated that they alter the rate of decline.

The effects of drug treatment on prognosis

Antipsychotic drugs, both typical and atypical, appear to worsen cognitive decline in dementia (McShane et al., 1997; Ballard et al., 2005; Vigen et al., 2011) and, as discussed earlier, are associated with increased mortality (Schneider et al., 2005). They have also been shown to adversely affect patients with DLB (Dickson et al., 1988; McKeith et al., 1992; Ballard et al., 1998). It appears that while these widely prescribed drugs do show benefits in the short term for specific symptoms, there is a danger they may worsen patient status overall.

Whether treatment with either cholinesterase inhibitors or memantine delays time to institutionalization is an important one for individuals and from a health economics perspective, but is a difficult one to answer with certainty, though evidence exists that suggests such benefits are seen with both groups of drugs (Feldman et al., 2009, Lachaine et al., 2011). Similarly, there is evidence that use of cholinesterase inhibitors and to a lesser extent memantine is associated with prolonged survival, though not time spent in institutional care. It is possible therefore that any extra life associated with use is spent at home, an idea which is likely to appeal to patients, although other studies have reported conflicting results (Tan

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et al., 2018; Wattmo et al., 2016, Kazmierski et al., 2018; Zhu et al., 2013).

Potential disease-modifying drugs for Alzheimer's disease

All current treatment for Alzheimer's disease is symptomatic rather than disease modifying, i.e. it does not slow down the underlying pathological disease process. As Alzheimer's is a disease largely of old age, delaying its onset and progression may have significant personal, societal, and economic benefits. For example, one study estimated that delaying progression to frank dementia by five years would result in a 41% lower prevalence and 40% lower cost of AD in 2050 (Zissimopoulos et al., 2014).

Efforts at disease-modifying treatment have targeted the pathogenic proteins associated with the disease and, in particular, beta amyloid. Enthusiasm for these treatments has been enhanced by the possibility to visualize amyloid in vivo and therefore the possibility of having a readout of target engagement in conjunction with clinical outcomes. Most trials of this sort have used passive immunization to varying species of beta amyloid using monoclonal antibodies. Results have been mixed. Early studies of bapineuzumab suggested that cerebral amyloid load as measured by Pittsburgh compound B PET scanning was decreased (Rinne et al. 2010). Disappointingly, early results from phase III trials of solanezumab and bapineuzumab failed to show significant cognitive or functional benefit from treatment despite replicating the earlier PET findings and there were safety issues with regard to cerebral oedema (Salloway et al., 2014; Doody et al., 2014). Possible reasons for failure of these studies including treating too late in the disease course, though sadly a trial of gantenerumab in prodromal disease was also discontinued due to futility and a further large trial of solanezumab in mild disease also failed to reach significance in its primary endpoints (Ostrowitzki et al., 2017; Honig et al., 2018). More hopeful results for a monoclonal antibody targeted to soluble amyloid fibrils (BAN2401) in mild disease demonstrated dramatic reduction of amyloid load on PET and improvement in cognition. Further studies of this antibody are awaited. Immunotherapy has also been targeted against tau, and early studies have reported promising immune responses to an active vaccine (Novak et al., 2017).

An alternative approach targeting amyloid involves inhibition of the enzyme beta secretase. This is one of the enzymes required to cleave amyloid precursor protein in to the toxic 40-42 amino acid species that aggregates in AD, and as such is suitable target for drug action. In a story that echoes that of the anti-amyloid monoclonal antibodies, early readouts looking at decreased levels of amyloid in the CSF looked promising, but this has failed to be replicated in large phase three clinical trials, for example, the recently reported failure of verubecestat to improve cognition or function in mild-to-moderate disease (Egan et al., 2018).

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A further approach is to target protein aggregation and one drug long touted as an antiaggregant of tau is leuco-methylthioninium, a derivative of methylene blue, though this drug may also have other beneficial effects involving tau phosphorylation and mitochondrial function. A recently published large clinical trial demonstrated no benefit on cognition or function of this drug compared to placebo overall. Intriguingly there did seem to be improvement in those patients taking it as monotherapy but no benefit to those taking it concomitantly with acetylcholinesterase inhibitors, despite it having no known effect as a cholinesterase inhibitor itself (Gauthier et al., 2016). Results of further investigation are awaited.

The similarity shared by many dementing illnesses, for example, protein misfolding and aggregation leading to cellular dysfunction and ultimately neuronal death, raises the possibility of applying therapeutic strategies that tackle these processes identified in other diseases. Examples include up-regulation of autophagy (a natural cellular process which clears misfolded proteins), inhibition of chronically activated unfolded protein response (another natural cellular response to the production of misfolded proteins), or targeting of neuronal death or inflammatory responses (Boland et al., 2018; Hughes and Mallucci, 2019). These alternative therapeutic approaches are beginning to be reflected in early clinical trials (Scheltens et al., 2018; Underwood et al., 2017). Other drugs are being trialled as a result of the overlap between AD and other diseases; for example, diabetes where more than one large trial is underway of the long acting GLP-1 agonist liraglutide. The overall picture provides reasons to be optimistic in a field that has had problems with repeated disappointment. Firstly, the sheer diversity of therapeutic approaches is encouraging—if the underlying therapeutic strategy of the current trials was the same then overall failure would be perhaps more likely. While diversity of approach to tackling the disease is welcome, attempting to make trials more uniform in their outcome measures will help in evaluating different approaches and to this end recent attempts to provide a consensus on outcome measures are welcome (Webster et al., 2017). Secondly, the translation of excellent basic science into clinical studies coupled with investment to connect patients and research initiatives such as the Clinical Research Network, Join Dementia Research, and dementia drug discovery institutes in the UK means that high-quality, large-scale clinical studies are possible and being performed. Together these changes are intended to bring forward the realization of a disease-modifying drug that could be rapidly available for widespread clinical use.

Conclusion

The pattern and progression of AD is highly variable. Predictors of decline include severity of illness, which predicts a more rapid course, and extrapyramidal and psychotic symptoms, which probably also do so. While antipsychotic drugs are of benefit in the short term in treating some non-cognitive symptoms, their long-term use may worsen the prognosis; cholinesterase inhibitors, on the other hand, improve

symptoms in the short term, but their effects in the longer term on the disease are unclear. There remains a pressing need to develop new symptomatic therapies in AD as well as viable disease-modifying agents.

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Vascular and mixed dementia

Chapter: Vascular and mixed dementia

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Introduction

Vascular disorders have been established as the most important 'environmental' risk factors for late-life dementia in Western settings because of their high prevalence and potential for modification. Historically, however, 'vascular dementia' (VaD) as a construct has attracted substantially less research than Alzheimer's disease (AD). This is partly because it falls between traditional clinical specialties, being seen as the province of stroke researchers by those interested in dementia, and vice versa, but more fundamentally because its validity as a 'diagnosis' has remained elusive. Research diagnoses tend to prioritize reliability over validity (since the former is more easily established) and can sometimes fail to keep up with accumulating knowledge about a clinical condition, or fail to reflect changing presentations. VaD has been a good example of this failure.

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Definitions of vascular dementia

Changing fashions for ‘lumping’ or ‘splitting’ dementia are fundamental to the problems underlying VaD as a diagnosis. Throughout the first half of the twentieth century, later-onset (‘senile’) dementia was viewed as an inevitable consequence of ageing and, since atherosclerosis was a popular substrate for ageing, most dementia was assumed to be ‘vascular’. Seminal post-mortem studies in the 1960s and early 1970s challenged this by demonstrating the importance of Alzheimer pathology—previously assumed only to underlie rare early onset (‘presenile’) syndromes. However it was evident that multiple cerebral infarctions were also responsible in some cases of cognitive decline, and a second ‘diagnosis’ of multi-infarct dementia arose, later to be subsumed under the more broad category of VaD.

One of the first structured assessments for VaD to come into widespread use in research settings was the Hachinski Ischemic Scale (Hachinski et al., 1975), although this was never intended as a diagnostic instrument and was simply a checklist of 13 features of ‘arteriosclerotic psychosis’ from a widely read textbook (Mayer-Gross et al., 1969); some refer to the course of the dementia (e.g. abrupt onset, stepwise deterioration, fluctuation), some to symptoms (e.g. nocturnal confusion, depression, somatic complaints), and some to the likely presence of or risk for cerebrovascular disease (e.g. history of strokes or hypertension, focal neurological signs). No attempt was made to validate the instrument or to investigate its scaling properties or the validity of the different weights given to some items. Despite this, it was found to have the highest inter-rater reliability in an independent evaluation of case identification instruments for VaD (Chui et al., 2000), probably because it primarily seeks to ascertain whether significant cerebrovascular disease is present in the context of dementia, rather than whether it is deemed to be causally related.

Considering the standard current classification systems for clinical practice, DSM-IV criteria required the presence of dementia and either focal neurological signs/symptoms, or evidence of cerebrovascular disease judged to be aetiologically related (American Psychiatric Association, 1994); this was having dropped the requirement for an early step-wise course of decline after DSM-III-R. For DSM-5 major and mild neurocognitive disorders (American Psychiatric Association, 2013), the classification of ‘vascular’ is recommended in individuals with clinical features suggestive of a vascular aetiology (mentioning onset following a cerebrovascular event and/or decline in complex attention and frontal-executive functioning) where there is evidence of cerebrovascular disease from history, examination, or neuroimaging. Probable and possible categorization is applied depending on number of these criteria fulfilled. The former bring the construct closer to VaD defined by ICD-10 criteria, which require both evidence of focal brain damage and evidence of

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cerebrovascular disease judged to be aetiologically related, as well as an uneven distribution of cognitive deficits.

Probably the most widely used criteria in research settings to date have been those developed in a 1991 workshop of the Neuroepidemiology branch of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN, (Román et al., 1993). A diagnosis of VaD using NINDS-AIREN criteria rests on evidence of cerebrovascular disease (both clinical and from neuroimaging), and an observed relationship between cerebrovascular disease and dementia (such as an onset within three months of an acute stroke or an abrupt deterioration in cognitive functioning, or a fluctuating or stepwise deterioration). A 'probable' diagnosis using this system requires all three of these criteria to be present while a 'possible' diagnosis can be made in the following situations: i) where dementia is accompanied by focal neurological signs in the absence of neuroimaging data; ii) in the absence of a clear temporal relationship between clinical stroke and dementia; iii) 'in patients with subtle onset and variable course of ... cognitive deficits and evidence of relevant CVD' (Román et al., 1993).

The system of subdividing dementia based on assumed underlying causation therefore continues to be enshrined in current diagnostic schedules. However, several changes over the 30–40 years since the first criteria were developed highlight problems with this approach when it comes to conceptualizing VaD:

- 1. *Changing cohorts.*** Older people dying in the 1960s lived through times when there was little opportunity to prevent or control cerebrovascular disease. More severe and florid pathology would have been observed at post-mortem than would be expected (in developed nations) today and was more clearly a primary cause of a dementia syndrome. However, people with dementia known to clinical services are now frequently in their ninth and tenth decades where underlying pathology is much more likely to be mixed. Most people in these age ranges will have at least mild levels of cerebrovascular disease which may be coincidental, or at least not a single causal factor.
- 2. *Advances in neuropathology.*** Early studies predominantly focused on multiple cortical infarctions. Other more subtle forms of cerebrovascular pathology, e.g. lacunar infarction, white matter disease, vascular amyloid deposition, and microangiopathy, have subsequently been highlighted. These may increase the risk of dementia but may not in isolation be sufficient to cause the clinical presentation; instead, a combination of pathological processes may be necessary.
- 3. *Advances in neuroimaging.*** Clinical diagnostic criteria for multi-infarct or VaD traditionally relied on a history of vascular risk factors, a history suggestive of recurrent strokes, and evidence on clinical examination of neurological deficits indicative of cortical

stroke. Subsequent technological advances allow in vivo identification of much more subtle changes, e.g. white matter hyperintensities and alterations in patterns of perfusion and connectivity. However, these are all common in unaffected people in old age and cannot be assumed to be causal when they are seen in someone with dementia.

Problems with 'vascular dementia' as a diagnosis

The validity of VaD as a diagnosis rests on the demonstration of a discrete syndrome (dementia) with a clear primary cause ('vascular'), and with good clinical and clinico-pathological reliability. Considering routine diagnostic practice, it is important to be aware that these criteria are problematic in a number of respects:

1. The clinical course of dementia (i.e. 'stepwise' vs 'gradual deterioration') is a poor predictor of pathological findings (Fischer et al., 1990).
2. Dementia following clinical stroke frequently shows a gradual deterioration and has been found to occur without further infarction in many, if not the majority of, cases (Kokmen et al., 1996; Tatemichi et al., 1994). Consistent with this, post-stroke dementia was found to be more strongly predicted by medial temporal atrophy and thalamic infarcts rather than NINDS-AIREN neuroimaging criteria (Firbank et al., 2012), or white matter hyperintensities (Firbank et al., 2007).
3. Risk factors for stroke have long been recognized to be risk factors not only for VaD but also for clinical AD (Stewart, 1998).
4. Dementia in community samples is frequently associated with mixed rather than discrete pathology (Holmes et al., 1999) and cerebrovascular disease seems to be rarely associated with dementia in the absence of Alzheimer pathology (Hulette et al., 1997).
5. Research diagnostic criteria poorly reflect underlying pathology. Although cerebrovascular pathology is likely to be present in cases with a previous diagnosis of VaD, it is also frequently present in people with other clinical diagnoses (Fernando et al., 2004; Holmes et al., 1999; White et al., 2005).
6. Clinical diagnostic criteria for VaD have poor inter-rater reliability (Chui et al., 2000; Lopez et al., 1994). Highest agreement is found where criteria simply estimate the degree of cerebrovascular disease in people with dementia (Hachinski et al., 1975), and unsurprisingly much lower agreement is found if a judgment is required as to whether dementia was actually caused by cerebrovascular disease. Different diagnostic schedules also show poor agreement with each other (Chui et al., 2000).
7. Operational definitions of dementia have been criticized for focusing excessively on memory impairment and for poorly reflecting cognitive impairment relating to vascular disease which more often affects non-memory domains such as executive function (Bowler and

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Hachinski, 2000), although this has been addressed to some extent in DSM-5.

The principal reason that dementia categorization has persisted is because of potential utility in AD research. If risk factors for a particular pathological process are to be identified, there is some rationale for excluding people with evidence of any other pathology. This can be readily carried out for AD since levels of vascular pathology can be reasonably estimated (and screened out) by clinical examination or neuroimaging, although neuropathologically 'pure' AD is less common than diagnostic criteria would suggest (Fernando et al., 2004). The same is not true for VaD. The only means of defining 'pure' VaD is to establish a temporal relationship between stroke episodes and cognitive decline, and then to exclude cases with evidence of gradual decline in between strokes. This process relies heavily on retrospective and potentially inaccurate information.

The implications are becoming increasingly problematic. If VaD as a diagnosis poorly reflects underlying pathology and relies on a differentiation from AD, which involves a large degree of subjective judgment and 'guesswork', then research attempting to apply these criteria is fraught with methodological shortcomings. Prevalence studies will be difficult to interpret if between-site equivalence cannot be assumed. Furthermore, any observed between-site differences in prevalence (or in the proportion of dementia defined as 'vascular') may simply reflect underlying differences in stroke incidence or local clinician diagnostic practice. Case control studies become difficult if all VaD cases have evidence of cerebrovascular disease by definition (or if it is absent or minimal in the case of AD) since they will differ from controls by definition.

One of the most important consequences of the 'diagnosis problem' has been that the role of vascular factors in dementia has historically been underestimated. If vascular factors are not often associated with dementia in isolation (i.e. other coexisting pathology is required), this does not mean that they are not important risk factors. The following sections review some of the evidence for this and discuss potential causal pathways, before considering potential implications for the treatment and prevention of dementia.

Specific 'vascular dementia' syndromes

If VaD and AD are not clearly distinguishable disorders, the continued usefulness of a sub-categorizing diagnostic system is questionable. However, this primarily applies to older age groups where overlapping pathology is likely. People who develop dementia relatively early (for example, in their seventh decade or younger) are much more likely to have a single underlying cause, and it therefore remains appropriate to sub-categorize dementia in younger-onset cases. Furthermore, there are particular syndromes within the 'VaD' category that can reasonably be

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considered as discrete diagnoses. These include genetic disorders such as 'cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy' (CADASIL), a familial disorder manifesting as recurrent strokes (most often lacunar infarcts) usually in the fourth to sixth decades, occurring in the absence of vascular risk factors and associated in most cases with a subcortical dementia and pseudobulbar palsy. The principal underlying pathology is an abnormality in basal smooth muscle cells, predominantly in the media of small cerebral arteries; and underlying mutations were successfully identified in the *Notch3* gene on chromosome 19 (Joutel et al., 1997). Other syndromes of familial VaD have been described (Box 31.1) and it is likely that, as with AD, further discrete disorders exist that may be explained by specific mutations.

Box 31.1 Examples of specific vascular dementia syndromes

Genetic disorders

Sickle cell disease

CADASIL

Hereditary cerebral haemorrhage with amyloidosis—Dutch and Icelandic types

Familial British dementia with amyloid angiopathy

Homocystinuria

Fabry's disease

Hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS)

Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS)

Strategic infarct dementia

Conditions associated with cerebrovascular pathology and secondary dementia:

Subdural haematoma

Systemic lupus erythematosus

Polyarteritis nodosa

Buerger's disease

Polycythaemia rubra vera

As well as genetic disorders, cases of dementia have been described that appear to have been caused by specific single ‘strategic’ infarctions (Tatemichi et al., 1992), most often within thalamic structures, the angular gyrus, or deep frontal lobe structures; these may also be considered as discrete diagnoses (Thal et al., 2012) because of the apparent single sufficient cause. In addition, of non-cardiovascular disorders causing secondary dementia, several do so through their effects on the vasculature (Box 31.1), although such disorders cause only a very small proportion of dementia cases.

Frequency of dementia occurring after stroke

Defining dementia after stroke presents semantic challenges—for example, in how to refer to a single major stroke that has caused substantial and permanent loss of cognitive function. However, these issues, and the limitations of VaD as a diagnosis, should not obscure the importance of vascular disorders as risk factors for dementia. There has been a helpful tendency for ‘post-stroke dementia’ research to consider all cognitive decline occurring after a stroke and accept that this encompasses a range of processes, from the *de novo* development of dementia as a result of the event to people whose stroke may be exacerbating pre-existing cognitive decline (vascular or otherwise).

Consensus estimates suggest that people with a history of stroke have a dementia prevalence of around 30%, representing a four- to sixfold increased risk. Prevalences following stroke range from 7% in community samples with first-onset stroke and excluding those with pre-stroke dementia, to 41% in clinical samples of recurrent stroke (Kalaria et al., 2016), although some level of persisting cognitive impairment is detectable in around 80% of cases (Jokinen et al., 2015; Mahon et al., 2017). A study following 355 older people (mean age 80 years) who were dementia-free at three months after stroke found an incidence of dementia prior to death in 23.9% over an average follow-up of 3.8 years (Allan et al., 2011)—considerably higher than the 2–3% per year incidence that would be expected in a community sample of that age range (Launer, 1998). The Framingham Study estimated a twofold increased risk over a ten-year period (Ivan et al., 2004), and this was found to remain raised over at least two decades after an index stroke (Kokmen et al., 1996). The twofold increase was supported by estimates from a systematic review (Savva et al., 2010), which also concluded that this was not accounted for by demographic factors or vascular risk profile. One study suggested a stronger association with cognitive impairment in the absence of dementia (Srikanth et al., 2004), but this may reflect differences in deciding the point at which mild cognitive impairment is distinguished from dementia (i.e. when it is believed to be affecting activities of daily living) in the context of a previous stroke.

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Selective mortality (in people with stroke who are at risk of developing dementia) is likely to be a diluting factor and to explain a stronger association in younger compared to older people (Ivan et al., 2004; Savva et al., 2010). High levels of variation between studies in reported prevalences of post-stroke dementia and appear to be due to differences in methodology: for example, whether the sample was hospital or community based and how rigorously pre-stroke dementia was ascertained and excluded. Over 90% of the variation was accounted for by methodology (Pendlebury and Rothwell, 2009).

Risk factors for post-stroke dementia

Clearly, any risk factor for stroke is also a risk factor for dementia caused by stroke (whether the stroke is the sole underlying cause or precipitates the clinical onset of dementia associated with other pathology). However, less is known about the factors that predict whether or not someone experiencing a stroke will go on to develop dementia. The first consideration is the nature of the index stroke itself. Although strategic infarct dementia syndromes have been identified, as described earlier, population-based studies have often failed to demonstrate a consistent association between stroke location and risk of dementia: for example with respect to arterial territories of cortical infarctions (Censori et al., 1996; Desmond et al., 2000; Pohjasvaara et al., 1998) and the location (or number) of lacunar infarctions (Loeb et al., 1992). Higher overall levels of cerebrovascular disease tend to predict development of dementia following stroke injury; these include the presence of previous stroke, multiple infarctions, silent infarcts, and white matter hyperintensities; however, predictors also include non-vascular brain lesions on neuroimaging, such as medial temporal lobe and/or global atrophy (Kalaria et al., 2016), again strongly implicating pre-stroke causal processes in many cases.

Other factors identified as being associated with risk of dementia following stroke (albeit not always consistently) are increased age, lower levels of education, previous stroke disease, and vascular risk factors such as diabetes, recent smoking, and atrial fibrillation (Barba et al., 2000; Censori et al., 1996; Desmond et al., 2000; Pohjasvaara et al., 1998). The role of blood pressure level is uncertain: although hypertension is clearly a risk factor for stroke, and therefore for stroke-caused dementia, many studies report no association between blood pressure at the time of stroke and subsequent dementia risk. Instead, risk of dementia has sometimes been associated with lower blood pressure and orthostatic changes (Pohjasvaara et al., 1998). Disorders associated with hypoxia and ischaemia (such as seizures, arrhythmias, and pneumonia) have also been found to be associated with higher risk of dementia after stroke (Moroney et al., 1996). A recent review concluded that there was supportive evidence for the following factors predicting post-stroke dementia: i) older age, female sex, and lower education among demographic characteristics; ii) pre-stroke cognitive decline and/or physical impairment; iii) haemorrhagic stroke, supratentorial stroke,

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dominant hemisphere stroke, and recurrent stroke; iv) infection, delirium, or early seizures following stroke; and v) imaging indicative of cerebral small-vessel disease, cortical atrophy, and medial temporal lobe atrophy (Mijajlovic et al., 2017).

Although prospective studies following a major stroke have been important in understanding dementia associated with cerebrovascular disease, they may not be generalizable to situations where multiple smaller infarctions have occurred. An early study with a different design investigated factors associated with dementia in a sample of people all of whom had multiple cerebral infarctions (Gorelick et al., 1993). Independent risk factors were: increased age, lower educational attainment, previous myocardial infarction, recent smoking, and lower systolic blood pressure. CT findings associated with dementia were: more severe stroke, left cortical infarction, and diffuse enlargement of the lateral ventricle suggesting cerebral atrophy (Gorelick et al., 1992).

Clinical features of post-stroke dementia

As mentioned, many cases of dementia following stroke appear to follow an Alzheimer-like clinical course and to occur without further episodes of infarction (Honig et al., 2003; Kokmen et al., 1996; Tatemichi et al., 1994). Pre-stroke cognitive decline is evident in many cases (Kase et al., 1998), and is associated with atrophic changes on neuroimaging, rather than early cerebrovascular disease (Pohjasvaara et al., 1999). In addition, not only does stroke predict cognitive impairment, but cognitive impairment is also associated with a raised risk of future stroke (Ferucci et al., 1996), and dementia following stroke predicts further stroke episodes (Moroney et al., 1997).

Taken together, this evidence suggests that there is a close (although potentially complex) interrelationship between stroke and primary degenerative changes underlying many cases of apparent VaD, and that the stroke itself may be a relatively late event in an ongoing process of insidious cognitive decline. One study found that the clinical picture shifted from one consistent with AD over the first two years after a stroke to a more classic 'VaD' picture over years two through four (Altieri et al., 2004). This is consistent with a process in which the stroke episode precipitates dementia in people with pre-existing Alzheimer pathology. Those without this vulnerability maintain their cognitive function initially, but remain at risk of further strokes and of dementia occurring at a later stage as a result of these.

A nested neuropathological follow-up in the cohort study reported by Allan and colleagues (2011) concluded that 75% fulfilled current VaD criteria. In this case, the exclusion of dementia at three months after stroke may have removed most of the 'precipitated AD' cases in favour of a more vascular picture. However, one should bear in mind that a neuropathological diagnosis is simply describing the relative extent of different pathological features, and conclusions are inevitably limited

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regarding which *one* of these actually caused the *ante mortem* clinical syndrome.

Taken together, these findings do suggest at least that Alzheimer pathology may be directly responsible for a reasonable proportion of dementia developing after a stroke and is consistent with estimations from clinical follow-up (Hénon et al., 2001). A post-stroke cohort is likely to yield high levels of cerebrovascular disease, which might be present in a person in the same age range who did not develop dementia, so causation should not be assumed from co-occurrence. Comparisons of neuropathological features between participants who did or did not develop dementia after stroke identified microinfarctions and medial temporal lobe atrophy as distinguishing features (Allan et al., 2011).

Vascular risk factors and dementia

Although clinical stroke is strongly associated with dementia, it does not appear to be the initiating event for cognitive decline in many cases. As discussed, pre-stroke dementia is detectable in a substantial minority of people with stroke, and milder pre-stroke cognitive decline may be more common still. A large body of complementary evidence now strongly suggests that risk factors for cerebrovascular disease are also risk factors for dementia—both due to AD and VaD, as estimated clinically.

Mid-life hypertension

Hypertension, a powerful risk factor for cerebrovascular disease, has long received attention as a risk factor for dementia (Stewart, 1999). However, it has taken time for consistent findings to emerge from prospective studies. These studies have had to involve large community cohorts (usually with at least 1000 participants) and at least ten to 15 years follow-up to demonstrate a risk effect, although even now there remain areas of variation, illustrated in the range of associations summarized in Box 31.2. Although most studies have analysed mid-life blood pressure as an exposure against late-life cognitive impairment or dementia as an outcome, it appears that it is a decade-plus interval between blood pressure measurement and dementia ascertainment that is important for demonstrating an association, rather than a younger age at blood pressure measurement, since delayed risk associations (over a 15-year follow-up) have also been found for late-life systolic blood pressure (SBP) and diastolic blood pressure (DBP) (Skoog et al., 1996).

Box 31.2 Examples of prospective associations between blood pressure and later cognitive impairment/dementia

Associations with worse late-life cognitive function

- Progressively higher mid-life diastolic blood pressure (DBP) (Kilander et al., 1998),

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- Raised mid-life systolic blood pressure (SBP) (≥ 160 mmHg compared to <110 mmHg) in men (Launer et al., 1995),
- Progressively higher mid-life SBP and DBP in people who had not received antihypertensive treatment (Elias et al., 1993),
- Persistently high SBP (≥ 140 mmHg) over a 38-year period (Swan et al., 1998),
- High SBP (≥ 160 mmHg compared to <140 mmHg) but not DBP (Kivipelto et al., 2001a).

Prospective associations with dementia

- Raised mid-life SBP and DBP ($\geq 160/95$ mmHg) in men for both dementia and AD, but only in those not previously receiving antihypertensive agents (Launer et al., 2000),
- Higher SBP at age 70 and higher DBP at age 70 and 75 for AD aged 85 (Skoog et al., 1996),
- Mid-life high SBP (≥ 160 mmHg compared to <140 mmHg) but not high DBP for AD (Kivipelto et al., 2001b),
- Both hypertension and 'pre-hypertension' (SBP/DBP $>120/80$ mmHg but not fulfilling hypertension criteria) defined by blood pressure levels and/or antihypertensive treatment (Gottesman et al., 2018),
- Orthostatic hypotension in people aged 80+ with hypertension (Peters et al., 2018).

Late-life hypotension

Cross-sectional surveys, on the other hand, have tended to find that people with dementia have lower blood pressure than those without, although this is not universally reported. Two large surveys in Sweden and US (Guo et al., 1996; Morris et al., 2000) found lower SBP and DBP in participants with dementia compared to those without. The first of these studies reported on both all dementia, and AD specifically (Guo et al., 1996), and the second just used AD as an outcome (Morris et al., 2000). On the other hand, one large survey of AD in Finland did not find any difference in blood pressure by dementia status (Kuusisto et al., 1997) and a survey in Japan found no difference in hypertensive blood pressure levels between participants with and without AD (Ueda et al., 1992).

Low blood pressure is common in older people and (for both SBP and DBP) known to be associated with adverse consequences (Boshuizen et al., 1998; Mattila et al., 1988; Satish et al., 2001). Hypotensive orthostatic blood pressure changes have also been found to be associated with dementia, in particular a reduced SBP response to standing (Vitiello et

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al., 1993), confirmed in prospective follow-up of an 80+ year old sample with hypertension (Peters et al., 2018). In a Swedish cohort without dementia, frontal and parietal atrophy was associated with lower SBP and parietal atrophy with lower DBP; those in the cohort with AD had lower SBP and DBP, and those with VaD had lower DBP (Skoog et al., 1998). Findings from several studies suggest that, for people with dementia, lower blood pressure level is also associated more advanced stage of the disease (Guo et al., 1996; Hogan et al., 1997; Skoog et al., 1998), suggesting that there may be effects of neurodegenerative disorders on blood pressure levels.

From those studies investigating *change in* rather than *level of* blood pressure, the following findings have been reported: i) an association between 30-year decline in SBP and worse psychomotor speed (Swan et al., 1998); ii) cognitive decline over a three-year period being associated with a 10mmHg SBP decline over the same period (Zhu et al., 1998); iii) dementia in women associated with a reduced level of SBP increase and a higher level of DBP decline over a ten-year period (Petitti et al., 2005); iv) dementia and AD associated with SBP and DBP decline over the previous three years (Qiu et al., 2004); v) dementia associated with a slower increase in SBP over the previous 15 years and consistently lower levels of DBP (Wagner et al., 2018); and vi) a 30-year cohort study of Japanese-American men finding that incident dementia at the end of the study associated with a greater previous increase in SBP from middle to late life and a more pronounced decline in SBP over a three- to six-year period prior to the clinical onset (Stewart et al., 2009).

Taking the above two sections together, there is therefore robust evidence that dementia is predicted by higher blood pressure ten to twenty years earlier, but that blood pressure undergoes an exaggerated decline in people with dementia over perhaps five years or so before the clinical onset of the condition. These observations appear to be exaggerations of changes expected with age (a rise in blood pressure up to and including midlife followed by a decline in later life) and, although evidence is less substantial, tend to be also observed for other vascular risk factors as described below.

Dyslipidaemia

Raised lipid levels have received less attention than blood pressure as risk factors for dementia and results are also conflicting. Some studies, predominantly from Scandinavian populations, have suggested that raised mid-life total cholesterol is associated with later dementia (Kivipelto et al., 2001b; Kivipelto et al., 2002; Kivipelto et al., 2005; Notkola et al., 1998). However, others have found over shorter periods of follow-up that higher total cholesterol levels are associated with lower risk of dementia (Mielke et al., 2005) or show no association at all (Reitz et al., 2004).

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In general, evidence supports associations between mid-life total cholesterol levels and risk of AD, but does not suggest associations with late-life cholesterol levels (Anstey et al., 2008) and findings from three studies have suggested an exaggerated decline in cholesterol levels from midlife to late life in people with dementia compared to controls (Mielke et al., 2010; Notkola et al., 1998; Stewart et al., 2007). However, this is not always found: another study found no trajectory differences for cholesterol sub-fraction or triglyceride levels (Wagner et al., 2018).

Diet and obesity

A large amount of attention has focused on dietary risk or protective factors for dementia. With many measures to choose from and a sizeable risk of false positive findings from multiple analyses, it is difficult to draw firm conclusions; however, there are several reports that an atherogenic diet is associated with increased risk (Kalmijn et al., 1997; Luchsinger et al., 2002), and a Mediterranean diet with lower risk (Féart et al., 2009).

As with cholesterol and blood pressure, the association between obesity and dementia has been complicated by the observation of changes in the risk factor (in this case, accelerated weight loss) prior to the clinical onset of dementia (Stewart et al., 2005). Initial studies suggesting that mid-life obesity measured by body mass index is a risk factor for dementia (Gustafson et al., 2003) were supported by a systematic review (Gorospe and Dave, 2007) and subsequent research (Hassing et al., 2009), including studies measuring central obesity (Whitmer et al., 2008). However, a large 26-year follow-up of an Icelandic sample found no association between mid-life obesity and a range of outcomes, including brain infarcts or microbleeds, total brain or white matter lesion volume, or dementia (Albanese et al., 2015).

Diabetes and metabolic syndrome

Type 2 (non-insulin-dependent) diabetes has also been found to be a risk factor for dementia, both VaD and AD (Ott et al., 1999; Peila et al., 2002). Selective mortality is likely to be important, reducing the co-occurrence of the two conditions, which may explain some negative findings (MacKnight et al., 2002). Strong interactions were reported between hypertension and diabetes as predictors of cognitive impairment in the Framingham Study (Elias et al., 1997). However, much of the effect of diabetes on risk of dementia appears to be independent of cerebrovascular disease and may involve other non-vascular pathways or common underlying factors (Stewart and Liolitsa, 1999). Indeed, the hypothetical links between the two conditions have been substantial enough for AD to be proposed as 'type 3 diabetes' (Steen et al., 2005).

Several studies have also reported associations between risk of dementia and the pre-diabetic state of insulin resistance or 'metabolic syndrome', either estimated through vascular risk factor clustering (Kalmijn et al., 2000) or directly measured hyperinsulinemia (Luchsinger et al., 2004). One study, however, found that both low and high insulin were associated

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with later dementia (Peila et al., 2004). In people with diabetes, there is some evidence for profiles associated with higher risk of cognitive decline and/or dementia. In one study, insulin treatment was associated with a higher risk of dementia (Ott et al., 1999) and mild cognitive impairment in another (Roberts et al., 2008), the latter study also finding associations of cognitive impairment with longer duration, earlier onset and complications. Possibly consistent with the association between insulin treatment and dementia risk, another study following a large cohort of people with type 2 diabetes found a higher risk associated with one or more hypoglycaemic episodes (Whitmer et al., 2009). However, another study found that dementia risk was predicted by both lowest and highest average glucose levels over five years (Crane et al., 2013) and there is evidence emerging implicating fluctuations or peaks in glucose levels in cognitive decrements, as well as diabetes complications such as macro- and microvascular disease (Biessels and Despa, 2018).

Smoking

Smoking has been implicated as a risk factor for dementia in numerous systematic reviews (Anstey et al., 2007; Hersi et al., 2017; Peters et al., 2008; Zhong et al., 2015). For example, Zhong and colleagues (2015) reported a risk ratio of 1.3 for all-cause dementia associated with current smoking, similar risk ratios for AD and VaD, a 34% increased risk for every 20 cigarettes per day smoked, and no increased risk of dementia outcomes for former smokers. A recent systematic review found a weak association between passive smoking and increased dementia risk (Stirland et al., 2017). Finally, it is worth noting a review concluding that studies with tobacco industry affiliation were more likely to report a protective effect for dementia and less likely to report a risk effect than studies without such affiliation (Cataldo et al., 2010).

Other vascular risk factors

Other vascular factors associated with dementia include ischaemic ECG changes (Prince et al., 1994), and atrial fibrillation (Ott et al., 1997), as well as measures of peripheral and carotid atherosclerosis (Hofman et al., 1997). Several studies have found that people who are more physically active (Laurin et al., 2001; Rovio et al., 2005; Yoshitake et al., 1995) or with higher cardiorespiratory fitness (Kurl et al., 2018) have a lower risk of dementia, which may or may not be mediated through effects on the vasculature.

Mechanisms of association

What is becoming increasingly apparent is that people at increased risk for stroke are also at increased risk for dementia, whether this is defined clinically as VaD (i.e. with evidence of significant comorbid cerebrovascular disease) or AD. The apparent associations with AD have not been clearly explained by missed infarctions (Ott et al., 1999) or by dementia with primary vascular pathology being misclassified as AD (Hulette et al., 1997), although these possibilities are difficult to exclude

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absolutely. Neuropathological studies of community populations have found very high prevalence of mixed vascular and Alzheimer pathology (Fernando et al., 2004), particularly in oldest age groups (Brayne et al., 2009; Corrada et al., 2012). An explanation therefore probably lies in links between vascular factors and AD. These may involve four possible pathways, which need not be mutually exclusive.

Interactions at a pathological level

Cerebrovascular pathology in dementia is reviewed elsewhere in this book (see Chapter 5). There are numerous theoretical ways in which vascular processes might induce or accelerate Alzheimer pathology, including amyloid deposition as a response to ischaemia, links through inflammatory pathways, blood-brain barrier disturbance secondary to cerebrovascular disease, and for diabetes, abnormal protein glycation secondary to prolonged hyperglycaemia.

These processes predict that people with vascular disease will have higher levels of Alzheimer pathology—a hypothesis that is difficult to test except in the rare instances where neuropathological follow-up has been carried out in people without dementia. An early study found that increased Alzheimer pathology was associated with hypertension or coronary artery disease in people without previous dementia (Sparks et al., 1995; Sparks et al., 1996). Elevated mid-life blood pressure was also associated with decreased brain volume and Alzheimer pathology in a cohort study with a relatively large pathological follow-up (Petrovitch et al., 2000). The same study also found associations between diabetes and increased Alzheimer pathology (Peila et al., 2002), although associations were found with a protective rather than atherogenic lipid profile (Launer et al., 2001), a finding which requires further clarification.

Associations were reported between smoking and neuritic plaques in a neuropathological follow-up nested within a large cohort study (Tyas et al., 2003), suggesting direct influences on AD for this exposure. Consistent with this, associations have been observed between smoking and PET amyloid positivity in vivo (Zhang et al., 2018); however, associations with reduced cerebral perfusion have also been reported (Siennicki-Lantz et al., 2008) in addition to the well-recognized adverse effects of smoking on cerebrovascular disease.

Not all studies have found consistent evidence for these types of associations—one community study found that raised blood pressure was associated with microinfarcts but not with other pathological changes (Wang et al., 2009) and another found less Alzheimer pathology among people who had been treated for hypertension compared to normotensive individuals (Hoffman et al., 2009). The large MRC CFAS community neuropathological study similarly found no associations between vascular risk factors and Alzheimer pathology burden, but instead implicated

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microinfarcts as the key underlying pathological pathway (Richardson et al., 2012).

As mentioned, a range of hypothetical links between diabetes and AD have attracted particular interest, besides the role of diabetes as a vascular risk factor. The concept of AD as 'type 3 diabetes', for example, rests on the following observations: brain insulin resistance and cognitive impairment caused by type 2 diabetes mellitus; disturbances in brain insulin and insulin-like growth factor signalling mechanisms as early abnormalities and potentially underlying AD lesions; experimentally induced 'brain diabetes' in animal models resulting in cognitive impairment and disturbed acetylcholine homeostasis; and responsiveness of these experimentally induced changes to insulin sensitization (de la Monte and Wands, 2008).

Clinical/symptomatic interactions

As well as acting directly on the progression of Alzheimer pathology, vascular disorders may also accelerate the onset of symptomatic dementia at relatively early stages of comorbid AD. In an early US study of elderly nuns who were screened in late life and followed to post-mortem, a lower level of Alzheimer pathology was observed in association with dementia if infarction was also present, suggesting that the infarction had accelerated the onset of dementia (Snowdon et al., 1997). Similar findings were observed around that time in the Oxford OPTIMA study, where early Alzheimer pathology was associated with much greater cognitive impairment if cerebrovascular disease was also present (Esiri et al., 1999). In another study using a community-derived sample, significant interactions were found between the presence of cerebral amyloid angiopathy and Alzheimer pathology in their association with previous level of cognitive impairment (Pfeifer et al., 2002). Other neuropathological follow-up studies of community samples have suggested a predominance of mixed pathology (Fernando et al., 2004), with independent influences of Alzheimer and non-Alzheimer pathology on cognitive function (White et al., 2005) or on the likelihood of dementia at death (Matthews et al., 2009).

One way in which vascular factors may influence AD is that memory impairment secondary to early Alzheimer pathology may be more likely to be noticed as 'dementia' if other cognitive domains are also affected. White matter disease may be important in this respect since subtle disruption of fronto-subcortical pathways may result in impaired executive function. White matter hyperintensities on magnetic resonance imaging are common in older age groups and are associated with vascular risk factors, particularly hypertension. Although they are more common in dementia and, across a population, are associated with relative cognitive impairment (Breteler et al., 1994), at an individual level they may be severe without any apparent clinical manifestations (Fein et al., 1990). They do not therefore appear to be sufficient in themselves to

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cause dementia but may precipitate this in the presence of other pathology—i.e. in effect, reduce the age of dementia onset.

Common underlying factors

An association between vascular disease and AD may be explained by a common underlying risk factor. Both vascular status and dementia have causal processes operating across the life-course with ample opportunity for interaction at many stages (Table 31.1). However, most research fails, or is unable, to take this into consideration and is potentially limited by focusing at a very late stage in long-term evolving processes. Vascular risk factors such as hypertension and diabetes are commonly classified as 'environmental' risk factors for dementia. However, they are known to have a substantial familial aetiology and it is possible that common genetic factors explain some of their association with AD. Lifestyle factors such as diet, physical activity, and personality could also potentially underlie later associations.

Table 31.1. A life-course model of the relationship between vascular factors and dementia

Infancy and childhood	Genetic factors determining later vascular risk and cognitive impairment Environmental stressors affecting both vascular risk (e.g. blood pressure, proneness to obesity) and cognitive function (level of attainment in childhood and/or vulnerability to later neurodegeneration)
Early adulthood	Level of 'attained' cognitive function set determining risk of later impairment ('reserve') Socioeconomic status influencing vascular risk profile, and risk behaviour (smoking, diet, physical activity)
Midlife	Vascular risk factors becoming manifest (hypertension, obesity, dyslipidaemia) Possible subtle early cognitive changes secondary to vascular damage; also very early Alzheimer and vascular pathological changes Continuing manifestation of lifestyle-related risk factors (diet, smoking, exercise)
Late life	Impact of clinical cerebrovascular disease (stroke, TIA) on cognitive function Co-occurring or consequent AD Metabolic changes associated with frailty (e.g. weight loss, decline in blood pressure) possibly exaggerated in pre-clinical and clinical dementia

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	Chronic effects of raised vascular risk (e.g. diminished blood pressure reactivity) Selective mortality (survivors with vascular risk factors potentially at lower risk due to other unknown protective factors)

‘Mendelian randomization’ studies attempt to identify causal associations through investigating genetic propensity to a risk factor as the exposure to, rather than the presence of, the risk factor itself. A recent review of such studies in dementia research concluded that the most convincing causal evidence was for shorter telomere length associated with AD, with only tentative evidence for smoking quantity, vitamin D, homocysteine, SBP, fasting glucose, insulin sensitivity, and high-density lipoprotein cholesterol; however, the key deficiency appeared to be in the size and quality of source studies (Kuzma et al., 2018). Both cognitive function and risk of vascular disease are determined by socioeconomic status from childhood onwards and at least part of the overlap in later life may reflect long-standing social inequalities—a mechanism which has tended to be ignored in preference to biological links.

Effects of Alzheimer’s disease on the vasculature

As well as vascular influences on Alzheimer pathology or its expression, it is also possible that AD induces or exacerbates cerebrovascular pathology. Even long-duration prospective studies cannot conclusively demonstrate the direction of causation if pathological processes begin one or two decades before clinical symptoms become manifest. Deposition of amyloid occurs in cerebral blood vessels as well as the brain parenchyma in AD. This ‘cerebral amyloid angiopathy’, described in detail in Chapter 5, is associated with both cerebral haemorrhage and small infarctions (Olichney et al., 2000), and is a common and apparently parallel pathology to parenchymal amyloid deposition (Keage et al., 2009). Abnormalities in capillary structure have also been reported in AD (de la Torre and Mussivand, 1993). It is therefore possible that the presence of AD may exacerbate or accelerate vascular pathology, or render the brain more vulnerable to further insults. Early cognitive decline may also affect factors such as diet, exercise, and adherence to prescribed medication, which, in turn, may influence the risk of cerebrovascular events.

Vascular risk factors and dementia treatment—clinical implications

In theory, clinical implications should be numerous since vascular disease is one of few potentially modifiable risk factors for dementia. However, although research attention is increasing in this area, there is woefully little direct evidence at present for any intervention to prevent or treat dementia through modifying vascular risk. Despite this, there are particular issues which can be addressed to some extent.

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Treatment of dementia through modifying vascular risk

If vascular disease were to cause dementia through damaging the brain directly, or through accelerating the progression of Alzheimer pathology, then it is likely that these processes would continue to contribute to the progression of disease after diagnosis. Interventions to halt or slow the progression of vascular disease could therefore be expected at least to prevent further cognitive decline, and possibly even improve cognitive function.

However, there has been little research into potential interventions. Even for aspirin, despite recent enthusiasm from animal models (Chandra et al., 2018) few randomized trials in dementia have been attempted. A pilot study in multi-infarct dementia reported improvement in cognitive scores and cerebral blood flow, although the protocol did not involve a placebo and participants were not blind to their allocation (Meyer et al., 1989). Another study found that men at high risk of cardiovascular disease who had received warfarin or aspirin had better cognitive function at the end of a five-year trial period than those receiving placebo, although cognition had not been assessed at baseline (Richards et al., 1997). A report of two further trials of aspirin in AD raised a concern of increased intracerebral haemorrhage, which was not balanced by any demonstrable effects on cognition (Thoonsen et al., 2010), and a systematic review concluded no proven benefit (Jaturapatporn et al., 2012).

Apart from drug treatments to reduce vascular burden, other lifestyle changes have received at least some consideration. There is randomized controlled trial evidence, for example, of a benefit of aerobic against anaerobic exercise on cognitive function in sedentary men (Kramer et al., 1999) and a beneficial effect of a six-month exercise programme over an 18-month follow-up period in participants reporting memory difficulties (Lautenschlager et al., 2008). However, recent trials have found no benefit of exercise in people with dementia on function, quality of life or carer burden (Lamb et al., 2018) or on global cognition or executive function (Toots et al., 2017), although a systematic review concluded that there was evidence of exercise training having benefit on depression in people with dementia (Barreto et al., 2015) and a subsequent trial of a hospital-based exercise programme reported benefits on agitation and lability (Barreto et al., 2015).

Considering treatment of vascular risk factors in dementia, a small randomized trial of different glucose control regimes in people with diabetes and dementia reported the best outcomes in the middle ranking intervention (i.e. better than the group receiving diet and exercise only, and better than those receiving assertive glycaemic control with oral medication and/or insulin; see Chen et al., 2017). However, the conclusion of a 2014 review of antihypertensive treatment in dementia concluded a lack of firm evidence for either benefits or harm, and recommended further research but caution in the meantime (van der Wardt et al., 2014). Further caution is warranted following the recent report of lower blood

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pressure during antihypertensive treatment being associated with accelerated cognitive decline, as well as higher mortality, in people aged 85+ (Streit et al., 2018).

Prevention of stroke in dementia

It is therefore uncertain whether modification of vascular risk in people with established dementia has an impact on the course of cognitive decline. However, there is also little evidence at present that such measures are contraindicated, aside from the need for caution inherent in any medication use for older and higher-frailty populations. The prescription of aspirin or the treatment of hypertension in a patient with dementia and cerebrovascular disease might be carried out not only in the hope of preventing further cognitive decline, but also to prevent stroke.

Complex ethical issues surround the question of how intensively to treat comorbid disease in individuals with clinical dementia, particularly when the dementia itself is at an advanced stage. In addition, although there may be no upper age limit for stroke prevention (Staessen et al., 2000), the effectiveness of interventions such as blood pressure control has not been adequately assessed in the context of comorbid multiple infarctions and dementia. However, it is important to bear in mind that, while some may consider an acute fatal stroke to be a preferable alternative to end-stage dementia, a non-fatal episode may lead to a lengthy period of disability and suffering, which might have been prevented. It is now accepted that intensive screening for preventable risk factors should take place in people with single or recurrent strokes. There is no good reason why people who happen to have dementia should be excluded from that process, although an undoubted problem with VaD has been its 'falling between stools' and the risk for people with this diagnosis receiving sub-optimal attention from both stroke and dementia services.

Treatment of dementia in people who have cerebrovascular disease

Although there is no good research evidence to suggest that 'VaD' and 'AD' can be adequately separated as distinct disorders, the persistence of the two diagnoses in clinical parlance has led to their incorporation in inclusion/exclusion criteria for clinical trials and, hence, to the perception that diagnosis determines treatment 'eligibility'. Although there is some trial evidence for a beneficial effect of acetyl-cholinesterase inhibitors in people with 'VaD', this is most evident for the sub-group with potentially mixed disease (Erkinjuntti et al., 2002) and a meta-analysis concluded uncertain benefit in the disorder as a whole (Kavirajan and Schneider, 2007). This may reflect previous findings suggesting that cholinergic deficits in pure VaD are not present, or are less strong than those in AD or mixed dementia (Perry et al., 2005; Sharp et al., 2009).

However, people with 'pure' VaD have also been very hard to identify, and the lack of detectable cognitive decline in the placebo group over the course of a standard trial means that treatment effects are hard to

demonstrate. The danger is that difficulties encountered in applying diagnostic criteria (which are predictable given the lack of evidence to support their applicability) limits enthusiasm for further trials in people with cerebrovascular disease and dementia resulting in an impoverished evidence base. Recommended indications for future treatments will be limited to AD alone because of a lack of evidence in other disorders. If dementia with cerebrovascular disease is classified as ‘vascular’ in clinical practice, then people with AD may fail to receive treatment on the basis of comorbidity.

Vascular risk factors and dementia—implications for prevention of dementia

The implications of current research for the prevention of dementia are substantial, whether vascular risk factors directly induce dementia pathology, or accelerate the onset of the clinical syndrome. However, effects may be difficult to demonstrate in conventional clinical trials because of the potentially long period over which risk factors exert their action, and the changed relationships between risk factor levels and dementia, closer to the clinical manifestation of cognitive decline. Furthermore, most interventions may be well established as beneficial for other reasons (e.g. preventing cardiac disease and stroke), so that it may not be possible ethically to have a placebo group, or to retain a double-blind placebo comparison, for a sufficient time period to test an impact on dementia incidence.

All of these issues may explain, for example, the frequently negative results for trials of antihypertensive agents on dementia as an outcome. A review of observational studies and trials combined concluded that there was suggestive evidence for benefits associated with calcium channel and renin-angiotensin system blockers (Rouch et al., 2015). This was supported by a later review of observational studies examining antihypertensives as a group and all-cause dementia as an outcome (Xu et al., 2017), and a recent trial of intensive blood pressure lowering showed benefits in secondary outcomes of mild cognitive impairment alone or combined with dementia, although the primary dementia outcome fell marginally short of statistical significance potentially because of early study termination (SPRINT MIND Investigators for the SPRINT Research Group et al., 2019)—another common challenge for preventative trials.

However, an alternative explanation for the lack of trial evidence for benefit is that observational evidence is broadly flawed for medications conferring benefits because of ‘confounding by indication’ (i.e. people receiving those medications having other protective factors). This may explain the lack of trial evidence for non-steroidal anti-inflammatory drugs, despite promising observational evidence for dementia risk reduction (Wang et al., 2015), as well as similar negative conclusions for statins in dementia prevention (McGuinness et al., 2016). Furthermore, as mentioned regarding blood pressure lowering, what is a beneficial intervention in midlife cannot necessarily be assumed to retain a positive

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benefit-risk ratio into later life, and further research is particularly needed in the most advanced age ranges where empirical evidence is least available.

If conventional cohort studies of vascular risk management are flawed (because of confounding by indication) and if adequately designed trials are unlikely to be feasible (because of the long period of observation required), it is possible that evidence will always be lacking on the scope for preventing dementia. However, it is worth at least considering imputation from parallel sources of evidence.

Specifically, if vascular disease is a risk factor for dementia then it can be hypothesized that populations with high levels of vascular risk will also have higher dementia risk. This has been supported in findings from UK African-Caribbean elders in whom dementia prevalence was raised 70% than UK-born counterparts and who also had higher prevalences of diabetes (Livingston et al., 2001). It is also supported by a recent national dementia survey carried out in Trinidad and Tobago, a nation known to have high rankings in diabetes and hypertension mortality, and where dementia prevalence was substantially raised, particularly in the 70–90 age range (Davis et al., 2018). It can also be hypothesized that improving vascular risk in a population over time will be reflected in subsequent decline in age-specific dementia prevalence and incidence, which again has received at least some support in Western settings (Matthews et al., 2013). Clearly there are other potential explanations for differences in dementia prevalence and incidence geographically and over time; however, there may be scope, with more evidence of this nature, to model the potential impact of moving a population from one level of risk to another in a way that is not currently possible with traditional research designs.

Conclusion: What is vascular dementia?

Vascular disease has long been recognized as an important cause of dementia. Current evidence supports this, even though vascular disorders are frequently not a single cause in isolation, but instead interact with other neuropathological processes. Renewed recognition of this and of the potential for prevention or treatment of dementia has resulted in welcome but long-overdue research interest and advice for those affected. VaD as a research field is therefore alive and well.

However, there remain major drawbacks with sub-categorizing dementia, 'VaD' being particularly problematic. Its continued usefulness is doubtful although there is uncertainty as to what should replace it. 'Vascular cognitive impairment' achieves a shift away from a memory-focused view of dementia. Even so, retaining the word 'vascular' still assumes that cerebrovascular disease can be separated out and identified as a single underlying cause of cognitive impairment. For clinical purposes, it may be most valid to consider dementia as the principal diagnosis and to include vascular disease as one of several potential predisposing, precipitating, or

maintaining factors. This approach is at least in keeping with the tradition of the diagnostic formulation and with the reality of multiple, interacting, and overlapping disorders (and causes for disorders) in older age groups.

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The Lewy body dementias: Dementia with Lewy bodies and Parkinson's disease dementia



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The Lewy body dementias: Dementia with Lewy bodies and Parkinson's disease dementia

Chapter:

The Lewy body dementias: Dementia with Lewy bodies and Parkinson's disease dementia

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Historical background

In 1817, James Parkinson described the clinical features of what he designated the shaking palsy, later renamed Parkinson's disease by Charcot. However, he did not describe a dementia syndrome in his patients, but stated that '... the intellect and senses are uninjured' (Parkinson, 1817). Fritz Heinrich Lewy (1885-1950) discovered in 1912 the intraneuronal eosinophilic inclusions, later named Lewy bodies, during his research on parkinsonism. In 1923 Lewy described 43 patients with parkinsonism of whom 21 were demented (Alafuzoff et al., 2009; Rodrigues e Silva et al., 2010), but dementia with Lewy bodies (DLB) was only first recognized as a neurodegenerative entity in 1961 when Okazaki described two clinical cases with dementia, disorientation, hallucinations, and profound motor symptoms with rapid

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progression with Lewy-body pathology (Okazaki et al., 1961). The triad of dementia, parkinsonism, and psychosis was considered the core syndrome, and later fluctuating confusion, frequent falls, neuroleptic sensitivity, and syncope were added. In 1998 α -synuclein (α S) was identified as the main constituent of Lewy bodies, designating a new group of neurodegenerative disorders named the α -synucleinopathies (Mueller et al., 2017; Spillantini et al., 1998) (see Table 32.1).

Table 32.1 α -synucleinopathies.

Name	Characteristic features
Dementia with Lewy bodies (DLB)	Dementia with parkinsonism, visual hallucinations, fluctuations, and/or REM sleep behaviour disorder (RBD)
Parkinson's disease (PD)	Tremor, rigidity, akinesia, and/or gait disturbance
Parkinson's disease dementia (PDD)	Dementia after more than one year of parkinsonian motor symptoms, i.e. Parkinson's disease.
Multiple system atrophy	Autonomic dysfunction, parkinsonism, and ataxia
Idiopathic REM sleep behaviour disorder	Acting out dream content during REM sleep
Pure autonomic failure	Orthostatic hypotension, constipation, urinary incontinence, sweating, and impotence

Nomenclature and clinical diagnostic criteria for dementia with Lewy bodies

Alzheimer's dementia (AD) pathologies such as tau-inclusions and in particular amyloid plaques are present in DLB, although usually to a lesser extent than in AD. Uncertainty regarding the contribution of underlying pathology to the clinical picture resulted in different groups designating different names for the same clinical phenomenon; diffuse Lewy body disease (Kosaka et al., 1984), dementia with cerebral Lewy bodies (Eggertson and Sima, 1986), or senile dementia of Lewy body type (Perry et al., 1990). The importance of Alzheimer pathology was stressed by other groups suggesting names like AD with Parkinson's disease

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changes (Ditter and Mirra, 1987), AD with incidental Lewy bodies (Joachim et al., 1988), and Lewy body variant of AD (Hansen et al., 1990).

In the early 1990s, both the Nottingham group (Byrne et al., 1991) and the Newcastle group (McKeith et al., 1992) proposed clinical diagnostic criteria for what later became DLB. In 1995 an international consortium developed the first consensus criteria for a clinical diagnosis of DLB (McKeith et al., 1996) characterized by dementia accompanied by the core features fluctuating cognition and consciousness, spontaneous features of parkinsonism, and recurrent complex visual hallucinations. Additional supporting features such as frequent falls, syncope, and transient loss of consciousness, systematized delusions, and severe sensitivity to treatment with antipsychotic drugs were listed. In the revised version of the criteria from 2005, suggestive features like REM sleep behaviour disorder (RBD) and a positive [(123)I]beta-CIT (2beta-carbomethoxy-3beta-(4-iodophenyl)tropane), SPECT(Single Photon Emission Computed Tomography (CIT-SPECT), or PET(Positron Emission Tomography) scan and neuroleptic sensitivity were added to the diagnostic criteria (McKeith et al., 2005). In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), major and mild neurocognitive disorder with Lewy bodies have been included alongside the other dementias corresponding to dementia with Lewy bodies and DLB-MCI, although without specific diagnostic criteria (American Psychiatric Association, 2013). In June 2017 the fourth consensus report from the DLB Consortium was published to include updated diagnostic criteria for DLB. These criteria now include core and suggestive clinical signs and symptoms, and additionally indicative and suggestive biomarkers. Hypersomnia and hyposmia are included in the supportive clinical criteria. The former category of suggestive features is no longer used. RBD is now included as a core clinical criterion, (see Table 32.2). Suggestive biomarkers have lower sensitivity and specificity as compared to the indicative biomarkers, and the suggestive biomarkers and supportive clinical criteria are not formally included in the diagnosis, but will when positive in the clinic support a clinical DLB diagnosis (McKeith et al., 2017).

Table 32.2 Diagnostic criteria for dementia with Lewy bodies (DLB)

Central feature Essential for a diagnosis of DLB is <i>dementia</i> , which is defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function, or with usual daily activities.	Core clinical features (The first three typically occur early and may persist throughout the course) • Fluctuating cognition with pronounced variations in attention and alertness. • Recurrent visual hallucinations that are typically well formed and detailed.

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Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent and occur early.	• REM sleep behaviour disorder (RBD) which may precede cognitive decline. One or more spontaneous cardinal features of parkinsonism: • Bradykinesia (defined as slowness of movement and decrement in amplitude or speed) • Rest tremor • Rigidity.
Probable DLB can be diagnosed if: Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or; Only one core clinical feature, but with one or more indicative biomarkers. Probable DLB should not be diagnosed on the basis of biomarkers alone. Possible DLB can be diagnosed if: Only one core clinical feature is present, with no indicative biomarker evidence, or; One or more indicative biomarkers are present but there are no core clinical features.	Indicative biomarkers: • Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET. • Abnormal (low uptake) of ¹²³iodine-MIBG myocardial scintigraphy. • Polysomnographic confirmation of REM sleep without atonia. Supportive biomarkers: • Relative preservation of medial temporal lobe structures on CT/ MRI images. • Generalized low uptake on SPECT/PET perfusion/ metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET images. • Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/ theta range. Supportive clinical features: • Severe sensitivity to antipsychotic agents • Postural instability • Repeated falls

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	• Syncope or other transient episodes of unresponsiveness • Severe autonomic dysfunction, e.g. constipation, orthostatic hypotension, urinary incontinence • Hypersomnia • Hyposmia • Hallucinations in other modalities • Systematized delusions • Apathy • Anxiety • Depression
DLB is less likely	In the presence of any other physical illness or brain disorder, including cerebrovascular disease, sufficient to count in part or in total for the clinical picture, although these do not exclude a DLB diagnosis, and may serve to indicate mixed or multiple pathologies contributing to the clinical picture, or; If parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia.
Adapted with permission from McKeith, I. G., et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. <i>Neurology</i>, 89(1): 88-100. Copyright © 2017, American Academy of Neurology. DOI: https://doi.org/10.1212/WNL.0000000000004058.	

Several preliminary reports suggested that the original consensus criteria had high specificity but low sensitivity (McKeith et al., 2000), but a systematically designed study with prospective validation against a pathological diagnosis found the criteria to have 83% sensitivity and 95% specificity. (McKeith et al., 2000). In another study from the Mayo Clinic, the criteria have been found to be more sensitive if RBD was included as a core feature (88%) or if probable DLB could be diagnosed with only RBD plus dementia (90%). The specificity in this study was 73% (Ferman et al., 2011). A study applying the 2005 clinical criteria found the

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sensitivity, specificity, positive predictive value, and negative predictive values for probable DLB compared to pathology to be 73%, 93%, 79%, and 90%, respectively (Skogseth et al., 2017). Both the diagnostic criteria from before 1996 (sensitivity 60.2% and specificity 93.8%) and the original consensus clinical diagnostic criteria from 1996 had low sensitivity against pathology from 19.4% in early stages up to 72.3% in later stages, with specificity from 64.3% to 95.1%. One possible explanation being poor recognition of fluctuations in the early criteria and not including RBD. The revised clinical and pathological criteria from 2005 performed reasonably well in a validation study including prospectively diagnosed cases applying a battery of standardized clinical instruments in 76 patients with the clinical diagnosis of either DLB or AD (Fujishiro et al., 2008). A meta-analysis of the 2005 criteria showed a sensitivity of 87.2% and a specificity of 74.5%. Diagnostic accuracy was calculated to 79.9% for criteria defined before 1996, 75.5% for the 1996 criteria, and 81.5% for the 2005 criteria. A tendency towards underdiagnosing DLB in earlier phases of the disease and over-diagnosing DLB in later disease stages was noted (Halliday et al., 2011; Nelson et al., 2010).

DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism. The term Parkinson's disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson's disease. In practice, setting the term that is most appropriate to the clinical situation should be used and generic terms such as Lewy body disease or Lewy body dementia are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing one-year rule between the onset of dementia and parkinsonism continues to be recommended (see McKeith et al., 2017).

Clinical diagnostic criteria for Parkinson's disease dementia

A Movement Disorders Society Task Force defined clinical criteria for probable and possible PDD (Emre et al., 2007) and later operationalization of these criteria for practical administration in the clinic with practical cognitive tests and suggested cut-off values has been published (Dubois et al., 2007; Goetz et al., 2008). The criteria define core and associated clinical features: The two core features are i) a diagnosis of PD according to Queen Square Brain Bank Criteria (Hughes et al., 1993), and ii) a dementia syndrome with insidious onset and slow progression with cognitive impairment in more than one domain representing a decline from previous level and impairment in activities of daily living (ADLs) independent of motor or autonomic symptoms. Associated clinical symptoms are i) cognitive features; impaired attention, executive functions, visuospatial functions, memory or language, and ii) behavioural features; apathy, changes in personality or mood like depression or anxiety, hallucinations, delusions, and excessive daytime sleepiness (EDS). Practical procedures for cognitive testing at different levels of diagnostic accuracy are defined; a score below 26 on the Mini-Mental State Examination (MMSE) as a global cognitive measure,

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reversed months test for attention, lexical fluency and clock drawing for executive function, MMSE pentagons for visuospatial functions, and three word recall from the MMSE as a test for memory. The authors suggest the Neuropsychiatric Inventory (NPI) to detect behavioural features and the clinical interview with a caregiver to diagnose EDS and explore ADL abilities (Dubois et al., 2007).

The MMSE is sub-optimal for DLB and PDD due to little focus on executive functions, and scales such as Montreal Cognitive Assessment (MoCA) and PD-Cognitive Rating Scale have been validated and recommended (Kulisevsky and Pagonabarraga, 2009). MoCA tests executive and visuospatial domains more thoroughly, scores can be compared to MMSE, and MoCA performs at the same level as MMSE regarding detecting deterioration of cognitive impairment over time in DLB (Biundo et al., 2016).

Mild cognitive impairment (MCI) and subjective cognitive decline (SCD)

In recent years, similar to AD, there has been increased focus on subjective cognitive decline (SCD) and MCI in PD and the early stages of DLB, i.e. subjective or objectively verified cognitive impairment without significant functional consequences. The exact time when dementia should be diagnosed can be difficult to determine in PD due to the fact that ADL difficulties can be caused by motor, sleep, and autonomic problems in addition to the cognitive failure. Little is known so far about SCD in PD, and there are as yet no established criteria and no described reliable method of capturing SCD in PD, possibly owing partly to the confounding effects of motor symptoms and non-motor symptoms. However, SCD has been reported in people diagnosed with PD, and can be a harbinger of cognitive decline among PD patients (Erro et al., 2014). 25–43% of non-demented PD patients have mild cognitive impairment (PD-MCI) (Aarsland et al., 2010), and 10–20% even at the time of diagnosis in *de novo* PD (Aarsland et al., 2009b; Elgh et al., 2009). In the ICICLE study the frequency of PD-MCI was as high as 42.5% using level 2 criteria at 1.5 standard deviations (SDs) below normative values, and in this study memory impairment was the most common cognitive domain affected, with 15.1% impaired in this domain at 1.5 SDs (Yarnall et al., 2014).

MCI is associated with shorter time to develop dementia in PD. However, there is a large variability between patients with PD-MCI as some of these will remain stable in terms of their cognition with some even reverting to normal cognition during follow-up. In one study, one in five PD patients with MCI had normal cognition on follow-up, but among those with persistent MCI the conversion rate back to normal cognition was much lower (Pedersen et al., 2013).

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Clinical diagnostic criteria for MCI in PD have been developed (Litvan et al., 2012). Typically, attentional and executive deficits occur early, but visuospatial and memory impairment are also common, and there is inter-individual heterogeneity in the cognitive profile (Barone et al., 2011; Litvan et al., 2011). There is some evidence that patients with different cognitive profiles differ in dementia risk; those with attention and executive deficits, usually due to fronto-subcortical dopaminergic lesions, may have a lower dementia risk than those with visual-constructive and semantic memory impairment, which is more associated with posterior and possibly non-dopaminergic lesions (Williams-Gray et al., 2007).

Three different subtypes of MCI have been described in DLB; i) cognitive, ii) behavioural and psychiatric, and iii) physical symptoms, and for the cognitive subtype both amnestic and non-amnestic MCI have been reported to precede DLB, with non-amnestic MCI most often converting to DLB (McKeith et al., 2016). Between 5–25% of MCI cases have been reported to convert to DLB in different studies (Donaghy and McKeith, 2014). DLB-MCI was found to be characterized by drooling, misjudging objects, and symptoms related to parkinsonism, fluctuating cognition, and RBD (Donaghy et al., 2017). Ferman and colleagues (2013) reported that among persons diagnosed with non-amnestic MCI, the progression rate to probable DLB was 20 events per 100 person-years among those with non-amnestic MCI.

Other pre-dementia DLB syndromes include idiopathic RBD (Claassen et al., 2010), primary autonomic failure (Larner et al., 2000), and somatoform disorder (Onofrj et al., 2010). Non-amnestic MCI patients with RBD had selective deficits in executive function and verbal memory, as well as a higher level of depressive symptoms in one study from Australia (Szeto et al., 2017). To conclude we have seen an increased focus on the MCI and MCI stages of both PD and DLB, and in this context formal research consensus diagnostic criteria for MCI in DLB have been recently published and include suggested biomarkers such as reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET, polysomnographic confirmation of REM sleep without atonia and reduced MIBG uptake on myocardial scintigraphy (McKeith et al., 2020).

Epidemiology

Dementia with Lewy bodies (DLB)

The prevalence and incidence of DLB are not known in detail, and DLB is often diagnosed as AD and dementia in PD is often not diagnosed. The proportion with DLB among those with late life dementia is around 10–22% (Aarsland et al., 2008b; Rongve et al., 2006; Zaccari et al., 2005). A study from 40 Swedish nursing homes with a mean study population age 86.0 ± 7.5 years reported the prevalence of DLB to be 16–20% in this population, depending on the degree of parkinsonism required for the diagnosis (Zahirovic et al., 2016). Studies from routine clinical settings typically report low frequencies of DLB, and in one recent report from the

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UK only 4.6% of the dementia cases were diagnosed as DLB in secondary care within the NHS (Kane et al., 2018). This has been a driver in the UK for the National Institute for Health Research DIAMOND Lewy Programme (improving the diagnosis and management of neurodegenerative dementia of Lewy body type), which focuses on improving the detection and management of DLB and PDD in clinical settings (Thomas et al., 2018).

Reports from research settings focusing on DLB typically report higher frequencies; a community-based survey from Japan, the Hisayama Study, found DLB in 10.6% of neuropathologically confirmed cases and pure DLB neuropathologically (i.e. Lewy body pathology alone with no co-pathologies) in 4.4% (Matsui et al., 2009). The Islington Community Study of Dementia from North London UK found 9.7% with a clinical diagnosis of probable DLB and 30.5% with possible or probable DLB combined (Stevens et al., 2002). A health survey of people 75 years and older in the Kupio area in Finland found the proportion of dementia cases diagnosed with DLB to be 21.9% (Rahkonen et al., 2003).

These three studies provide the best estimates of the prevalence of DLB in the general population and suggest that DLB accounts for 10–22% of the dementias in the 65+ age group, indicating that about 1% of the population over 65 years suffer from DLB. In a study from Western Norway applying the revised consensus criteria from 2005 on a referral cohort to old age psychiatry and geriatric medicine clinics in 2005–2007, 15.8% of persons with mild dementia were diagnosed with probable DLB (Aarsland et al., 2008b). In a systematic review of published population and clinical studies, 4.2% of all diagnosed persons living with dementia in the community fulfilled diagnostic criteria for DLB; in secondary care, this increased to 7.5%. The incidence of DLB was 3.8% of new dementia cases (Jones and O'Brien, 2014). These estimates are probably too low because many studies did not specifically focus on diagnosing DLB and did not use specific instruments to detect the core symptoms.

Parkinson's disease dementia (PDD)

Although originally considered to be relatively rare (Brown and Marsden, 1984), several more-recent studies reported that dementia is common in PD. A systematic review found that, in cross-sectional studies, more than 30% of PD patients have dementia (Aarsland et al., 2005b). Subsequent longitudinal studies reported a three- to six-times higher incidence of dementia in PD compared to non-PD subjects (Aarsland et al., 2003), and in two long-term studies it was shown that up to 80% of PD patients will eventually develop dementia (Buter et al., 2008; Hely et al., 2008), although lower dementia prevalence in a PD population of only 5% after four years has been reported elsewhere (Santangelo et al., 2015). In a cohort of persons diagnosed with PD and with normal cognition, 50% developed cognitive decline after six years of follow up (Pigott et al., 2015). In the CamPaIGN study, based on an incidence PD cohort, the incidence of dementia was somewhat lower, with less than 50% of the

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cohort having developed dementia eight years after diagnosis. The mean time to dementia in this study was 6.2 years, with old age, postural and gait disturbance motor type, and early cognitive impairment predicting shorter time to dementia (Evans et al., 2011). Different subtypes of PD have been identified based on the clinical course and neuropathology. The different subtypes have different risk of dementia during the different stages of the disease; older onset patients (>70 years old) were found to reach dementia earlier, with much shorter disease duration and have more α -synuclein in Lewy bodies in the brain, and possible age-related plaque pathology in the cortex. Persons diagnosed with DLB have the shortest disease duration, with substantive amounts of Lewy bodies and Alzheimer-type pathologies in the whole brain. According to the authors, these data suggest that two age-related factors influence pathological progression in Parkinson's disease: the age at symptom onset, and the degree and type of age-related Alzheimer-type co-pathology (Halliday and McCann 2010).

Molecular pathology

The combination of both Lewy pathology (Lewy bodies and Lewy neurites) and AD pathology (fibrillary β -amyloid and intraneuronal tangles consisting of hyper-phosphorylated tau) predicts dementia better than the severity of any single pathology alone, and those with the combination of amyloid and Lewy pathology have a faster cognitive decline and shorter survival and thus a more aggressive disease. α -synuclein can induce hyper-phosphorylation of tau and β -amyloid can also increase phosphorylation of α -synuclein, thus explaining the additive and synergistic effect of the two types of pathology. Hyper-phosphorylated proteins will more easily aggregate. The neuronal damage might stem from shorter fibrils of α -synuclein like the case in AD with β -amyloid. The Lewy bodies are found in specific brain areas associated with wide neuromodulatory functions (e.g. substantia nigra, locus coeruleus, and pedunculopontine nucleus) and peripheral nervous systems, and researchers now believe that these cells are particularly vulnerable for this type of pathology because of long and highly branched axons with high numbers of synapses (Weil et al., 2017).

A proposed theory combining these effects and converging on lysosomal processes establishes lysosomal function and lipid processing as crucial mechanisms in disease development in both PD and DLB. Different genetic risk factors (see Genetics) including overexpression of α -synuclein lead to oxidation of dopamine causing glucocerebrosidase (GBA) dysfunction and slowing of lysosomal digestion, and consequently, the accumulation of more α -synuclein. In this way the Lewy body diseases share aggregation of α -synuclein and formation of Lewy bodies and Lewy neurites as their common hallmarks of pathology. The normal structure and function of α -synuclein is not yet well known, but it is believed to be involved in synaptic plasticity. Increased expression of α -synuclein will inhibit synaptic reclustering after neurotransmitter release and thus

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inhibit neurotransmitter release in the synaptic cleft (Nemani et al., 2010).

Neuropathology

Different pathological staging-systems have been proposed for DLB, PDD, and PD. Kosaka and colleagues (1984) proposed to differentiate three subtypes of DLB pathologically on the basis of where the pathology is predominant: brainstem, transitional, and cortical. The revised pathological consensus criteria now implement severity and distribution of both Alzheimer and Lewy body pathology in the CNS in these three locations and defines the likelihood that the pathological findings are correlated with a clinical DLB syndrome as low, intermediate, or high (McKeith et al., 2017).

Braak and colleagues (2003) proposed criteria for staging the Lewy body pathology in PD and others have proposed models for DLB (Leverenz et al., 2008; Muller et al., 2005). Three distinctive groups have been described neuropathologically in dopa-responsive PD patients recruited and followed until death (Halliday et al., 2008); one group has younger onset PD and longer duration of disease with neuropathology distribution corresponding to the Braak stages (see Table 32.3). A second group is characterized by an early malignant dementia dominant syndrome and severe neocortical disease and thus is analogous to DLB. The third group consisted of persons who had older onset of PD, shorter survival, and a more complex disease with additional pathologies and higher Lewy body loads in the brain.

Table 32.3 Staging of Lewy body pathology in the human brain.

Reference	Year	Comment
(Kosaka et al. 1984)	1984	Group A: Diffuse type of LBD; cerebral cortex, basal ganglia, diencephalon, and brainstem affected by Lewy body pathology Group B: Transitional type between A and C Group C: Brainstem and diencephalon affected like in PD
(Braak et al. 2003)	2003	Stages 1-2: Presymptomatic; pathology confined to medulla oblongata and olfactory bulb Stages 3-4: Symptomatic phase; affection of the substantia nigra, midbrain, and basal forebrain. Stages 5-6: Cognitive failure and dementia, cortex affected.

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(G. Halliday et al. 2008)	2008	Group 1: Younger patients with distribution of pathology according to the Braak staging. Group 2: Early malignant dementia dominant syndrome Group 3: Older onset, shorter survival, and more pronounced Lewy related pathology.
(Beach et al. 2009)	2009	I Olfactory bulb IIa Brainstem predominant IIb Limbic predominant III Brainstem and limbic IV Neocortical

Genetics

In PD, the proportion of phenotypic variance that can be explained from known genetic risk loci has increased as more of the genetic variants underlying the disease have been discovered, with recent estimates exceeding 40% (Hamza and Payami, 2010). Forty-one different genetic loci are related to the common type of PD, with ten of these loci possibly including more than one related gene (Chang et al., 2017). These genetic loci and genes provide evidence of disease mechanisms in PD like accumulation of α -synuclein, tau-pathology, disturbances in lysosomal functioning including *GBA* (the gene encoding the lysosomal enzyme glucocerebrosidase), and the immune system. *SNCA*, *MAPT*, *LRRK2*, *GBA*, and *HLA* have been found to be among the most important risk genes for PD (Hardy, 2010; Nalls et al., 2011). On the other hand, the genetic underpinnings of dementia in PD have been much less studied. Increased dementia risk in family members of people with PD has been reported (Kurz et al., 2006); associations between dementia and mutations in *MAPT* (Seto-Salvia et al., 2011) and *PSEN2* (Meeus et al., 2011) have also been reported, and Williams-Gray and colleagues (2009) found conflicting results regarding *APOE*. *GBA* is related to a 2.4-fold increase in the risk of cognitive impairment and dementia in PD (Creese et al., 2017). Previously known mutations in AD and PD have been found in both PDD and DLB and suggest a genetic overlap in these conditions (Guerreiro et al., 2016; Meeus et al., 2011).

In some families, DLB has been found to occur as an autosomal dominant heritable disease due to *SNCA* duplication or triplication, i.e. the gene coding for α -synuclein (Johnson et al., 2004). Traditional genetic studies have identified multiplications (Chartier-Harlin et al., 2004; Singleton et al., 2003) and mutations in the gene encoding α -synuclein (*SNCA*) (Brown, 1997; Yamaguchi et al., 2005; Zarranz et al., 2004) and β -synuclein (*SNCB*) (Ohtake et al., 2004).

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DLB is, however, typically late onset (i.e. after 65 years of age) and sporadic, and the heritability was, until recently, estimated at 36% with substantial genetic overlap with both AD and PD (Guerreiro et al., 2016; Guerreiro et al., 2018b). New and better methods and improved power due to a higher number of included cases have increased the heritability of DLB to 60%, i.e. in the same scale as in AD (Guerreiro et al., 2018). Indeed, genetic studies have suggested associations of *APOE*, *GBA*, *SCARB2*, *CNTN1*, and *SNCA* with DLB in both clinically and neuropathologically diagnosed cases (Bras et al., 2014; Guerreiro et al., 2018b; Rongve et al., 2019). *GBA* mutations have been reported in 7.8% of persons diagnosed with DLB with an odds ratio (OR) of 8 for DLB in those carrying these mutations (more than in PD, where the OR is 6.5; see Nalls et al., 2013). Even higher frequencies of *GBA* mutations (up to 31%) reported in Ashkenazi Jews diagnosed with DLB suggest that *GBA* is a stronger risk factor for DLB than for PDD. Like in AD but with a weaker effect, the *APOE* $\epsilon 4$ allele increases and the *APOE* $\epsilon 2$ allele decreases the risk of developing DLB (Berge et al., 2014). Involved in the brain's cholinergic activity, the k-variant of the butyrylcholinesterase gene is associated with the risk of developing both AD and DLB and with an increased rate of cognitive decline in DLB (Vijayaraghavan et al., 2015). Moreover, whole exome sequencing studies have identified rare and pathogenic variants in *GBA*, *PSEN1*, or *APP* in 4.4%–25% of participants with pathologically or clinically diagnosed DLB (Geiger et al., 2016; Keogh et al., 2016). However, regarding the common variants, none of the AD associated risk genes identified in large genome wide association studies (GWAS) have been associated to DLB except for *APOE* $\epsilon 4$. In DLB it is still challenging to collect big cohorts for GWAS; nevertheless, such efforts are ongoing, and will most likely lead to many more genes being associated with the disease in the future.

Biomarkers

A variety of imaging, electrophysiological, blood, and cerebrospinal fluid (CSF) biomarkers have been studied as potential diagnostic markers between DLB and AD (Aarsland et al., 2008a). ^{123}I -N-3-fluoropropyl-2beta-carbomethoxy-3beta-4-iodophenyl tropane (^{123}I -FP-CIT SPECT) or DaTSCAN, the visualization of the striatal dopamine transporter, a measure of the dopaminergic pre-synaptic nigro-striatal system, is the first established biomarker in the Lewy body dementias (McKeith et al., 2007). A meta-analysis found a sensitivity of 86.5% and specificity of 93.6% (Papathanasiou et al., 2011). An abnormal scan could identify those patients with possible DLB who progressed to probable DLB after 12 months (O'Brien et al., 2009), and FP-CIT SPECT has also been validated against neuropathology (Fig. 32.1; see also Thomas et al., 2017).

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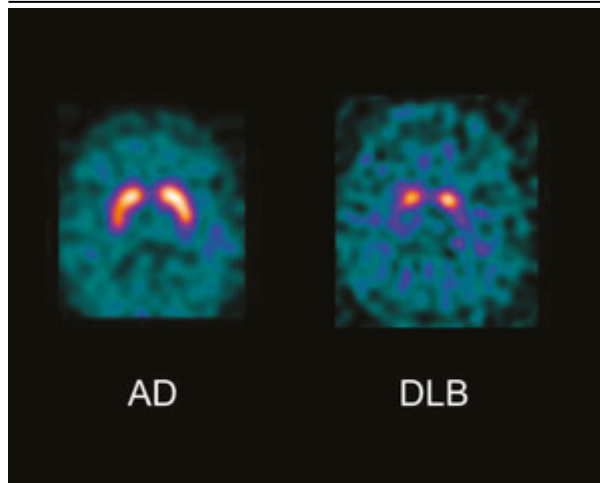


Fig. 32.1

FP-CIT SPECT images in autopsy confirmed AD and DLB.

Image on the right side from a person living with dementia with Lewy bodies (DLB) showing reduced uptake on both sides of the basal ganglia and most pronounced on the right side of the brain with no uptake in the putamen area and with normal uptake on both sides in the caudate nucleus and putamen areas in the person diagnosed with Alzheimer's disease (AD) on the image on the left side.

Reproduced courtesy of Dr. Sean Colloby, University of Newcastle, UK.

^{123}I -metaiodobenzylguanidine (MIBG) myocardial scintigraphy has been shown to reliably identify DLB even in mild cases (Suzuki et al., 2005), and is included as a supportive feature in the 2005 diagnostic criteria for DLB and as an indicative biomarker in the updated 2017 criteria. Both FP-CIT SPECT and myocardial scintigraphy can reliably differentiate PD from some other movement disorders (Hauser and Grosset, 2011; King et al., 2011).

Earlier studies found reduced perfusion in occipital cortical areas in DLB as compared to AD on perfusion SPECT-images. In a recent study relative preservation of cingulate glucose metabolism on PET imaging in the posterior cingulate gyri versus that in the precuneus had a 84.6% sensitivity and 84.6% specificity in discriminating DLB from AD (Imabayashi et al., 2017); see Fig. 32.2. Studies using glucose PET have found reduced metabolic activity in neocortex associated with cognitive impairment even early in PD (Pappata et al., 2011).

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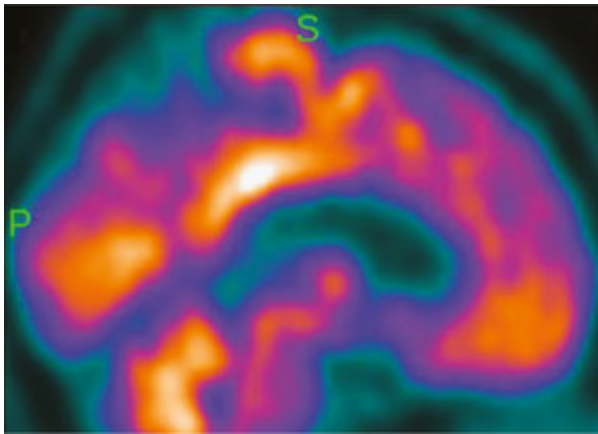


Fig. 32.2

PET imaging in DLB with posterior cingulate island sign.

Image showing a gap in the uptake in the cingulum between the parietal and occipital areas leaving a posterior cingulate island of uptake.

P; posterior. S; superior.

Reproduced courtesy of Dr Michael Firbank, Newcastle University, UK.

Structural imaging using MRI usually shows preservation of the medial temporal lobes in DLB as compared to AD, and this feature is now included in the revised diagnostic criteria as a supportive biomarker (Fig. **32.3**). Most studies of DLB and AD have reported low accuracy of this biomarker, but Burton and colleagues (2009) showed high accuracy, with sensitivity of 91% and specificity of 94%, in a prospective study with pathological verification of the clinical diagnosis. Watson and colleagues (2015) found alterations in cortical thickness in DLB, revealing relatively little grey matter thinning, with any changes predominantly affecting the posterior parietal areas in contrast to the temporoparietal pattern observed in AD. Subcortical volume changes on a group level have been noted in DLB with changes in left caudate, bilateral putamen, left thalamus, brainstem, and total subcortical grey volume, and these are more pronounced in DLB as compared to healthy subjects (Watson and Colloby, 2016; Watson et al., 2016). MRI has also demonstrated cortical atrophy in PDD (Beyer and Aarsland, 2008; Burton et al., 2005) and PD-MCI compared to cognitively normal PD patients. Atrophy of hippocampus and parietal-temporal cortex notably can also predict future cognitive decline in PD (Weintraub et al., 2011).

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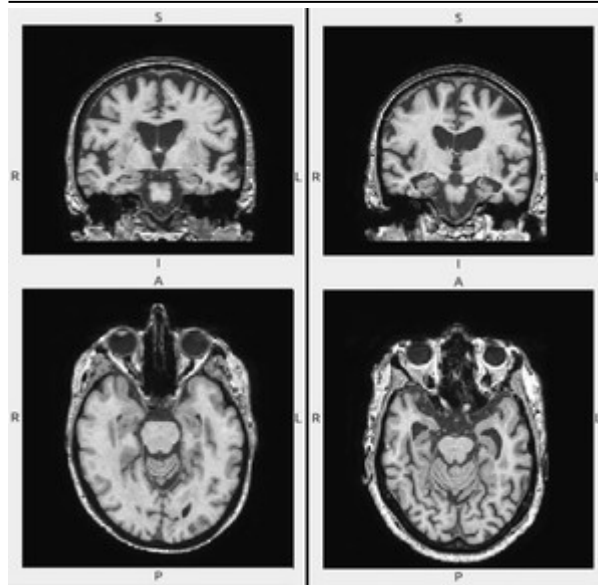


Fig. 32.3

Structural magnetic resonance image (MRI) of person with Dementia with Lewy bodies (DLB) (left side) with relative preservation of hippocampal volume and cortical structures compared to person with Alzheimer's disease (AD) (right side). Both patients were 78 years old males.

Reproduced courtesy of Dr Michael Firbank, Newcastle University, UK.

Promising findings have been reported also using quantitative EEG, with relatively more slowing of oscillatory brain activity in DLB and PDD compared to AD (Bonanni et al., 2008). Quantitative electroencephalogram (QEEG) methods are able to differentiate early DLB from AD, and QEEG may represent a powerful tool to predict the progression from MCI to DLB with a sensitivity and specificity close to 100% (Bonanni et al., 2015).

In AD, the concentration pattern of CSF proteins like beta-amyloid species such as amyloid beta 42 ($A\beta_{42}$), total tau, and p-tau have been found to distinguish between AD and normal controls (Mattsson et al., 2009). However, a change in the same direction has been shown in DLB, and thus the specificity against DLB is not high and CSF AD markers cannot presently be used to distinguish between AD and DLB (Mollenhauer et al., 2006; van Steenoven et al., 2016).

The concentration of α -synuclein, the key protein in DLB and PD, can be measured in CSF and plasma. Although lower concentrations have been reported in CSF in Lewy-body disorders, this cannot convincingly differentiate DLB from AD or normal controls as yet (Mollenhauer et al., 2011; Noguchi-Shinohara et al., 2009; Spies et al., 2009).

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Alves and colleagues (2010) found that low CSF concentrations of $\text{a}\beta_{42}$ in PD correlate with poor cognition in cross-sectional studies, particularly regarding memory. Siderowf and colleagues (2010) confirmed these findings in a longitudinal study showing that low CSF levels of $\text{a}\beta_{42}$ predicted significant cognitive decline during the next two years, and Abdelnour and colleagues (2016) reported similar findings in DLB. In contrast, amyloid imaging usually finds low amyloid load in PDD when compared to AD and DLB (Jokinen et al., 2010).

Clinical features of dementia with Lewy bodies and Parkinson's disease dementia

These include cognitive, neuropsychiatric, behavioural, sleep, motor, and autonomic symptoms (Table 32.4).

Table 32.4 Clinical symptoms in dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD).	
<i>Cognitive impairment</i>	Attentional Visuospatial Executive Memory Language
<i>Cognition</i>	Fluctuating
<i>Neuropsychiatric and behavioural symptoms</i>	Depression Apathy Anxiety Hallucinations Delusions Agitation Somatoform disorder Obsessive compulsive disorder
<i>Sleep disturbances</i>	REM sleep behaviour disorder Excessive daytime sleepiness Insomnia Restless legs syndrome Nocturnal leg cramps Obstructive sleep apnoea Sleep walking Periodic leg movements during sleep Sleep attacks Unintended sleep episodes

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<i>Motor</i>	Symmetrical or asymmetrical parkinsonian symptoms Bradykinesia Rigidity Resting tremor Postural instability Gait disorder
<i>Autonomic</i>	Orthostatic hypotension Syncope Incontinence Constipation Impotence

Cognitive profile

Persons diagnosed with DLB and PDD have prominent visuospatial and executive cognitive dysfunction in contrast to those living with AD. DLB patients are equally impaired in semantic/category and phonemic/letter fluency tests, whereas AD patients perform significantly better on the phonemic/letter fluency tests (Goldman et al., 2014). No specific cognitive test battery has been developed to screen for or diagnose DLB, but as noted previously, the MoCA screening test includes more tests for executive and visuospatial cognitive functions as compared to the MMSE and its use has been recommended in DLB and PDD (Nasreddine et al., 2005). A composite risk score including cognition has been developed for detecting DLB and discriminating DLB from AD and DLB-MCI from AD-MCI. In a consecutive series of 256 persons the mean Lewy Body composite risk scores (LBCRS) were significantly different between DLB and AD (6.1 ± 2.0 vs. 2.4 ± 1.3 , $P < .001$) and between MCI-DLB versus MCI-AD (3.2 ± 0.9 vs. 1.0 ± 0.8 , $P < .001$). The LBCRS was able to discriminate DLB from other causes of dementia. Using a cut-off score of 3, areas under receiver operating characteristic (ROC) curve for DLB versus AD = 0.93 (0.89–0.98) and for MCI-DLB versus MCI-AD = 0.96 (0.91–1.0). The score is composed of ten questions for the patient and caregiver. Questions 1–4 are taken from the Unified Parkinson's Disease Rating Scale, question 5 from the Epworth Sleepiness Scale, questions 6–7 from the Mayo Fluctuation Questionnaire, question 8 from the Neuropsychiatric Inventory, question 9 from the Mayo Sleep Questionnaire, and question 10 from physical findings and complaints of the patient. (Galvin, 2015). Although caregivers reported memory problems to be the most frequent initial symptom in DLB (Auning et al., 2011), most studies objectively report an initial impairment in visuospatial and executive cognitive domains. In a cluster analysis to group all types of mild dementia subtypes according to the level of parkinsonism, hallucinations, fluctuations, and RBD, a group of patients was identified with high scores for both parkinsonism, hallucinations, and

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fluctuations and consisted of exclusively patients diagnosed as having clinically DLB or PDD. This group scored significantly lower on tests for visuospatial cognitive skills as compared to the other three groups identified (Rongve et al., 2010b). From the same cohort, impaired verbal fluency was reported in those diagnosed with DLB, and tests where persons diagnosed with DLB performed worse than those with AD were highly correlated with degree of parkinsonism, but not with cognitive fluctuations or visual hallucinations (Brønnick et al. 2016). Hamilton and colleagues (2012) found that early visuospatial cognitive impairment predicts visual hallucinations in DLB. In longitudinal studies, Rongve and colleagues (2016) found a faster progression of cognitive decline in DLB as compared to in AD. In a review and meta-analysis three studies reported a faster cognitive decline on MMSE in patients with mixed DLB and AD compared to pure forms, whereas two studies reported a faster decline on delayed recall and recognition in AD and one in DLB on verbal fluency. Six studies were included in a meta-analysis that showed no significant difference in annual decline on MMSE between DLB (mean 3.4) and AD (mean 3.3) (Breitve et al., 2014). In DLB the progression of overall cognitive impairment is occurring at the same speed as in AD, and no cognitive domains have clearly been shown to worsen more rapidly in DLB in meta-analyses. However, clinical disease progression until nursing home placement is faster in DLB, and survival has been found to be shorter in DLB as compared to AD and other types of dementia (Strand et al., 2018).

In *de novo* diagnosed PD followed up after 36 months in the ICICLE-study, 8% of patients had developed a dementia all of which were previously PD-MCI. Applying level I criteria with MoCA scores of 26 or lower, 70% were cognitively stable, 19% cognitively declined, and 11% improved over 36 months. Applying level II criteria (at 1, 1.5, and 2 SD on cognitive tests), 25% were cognitively stable, 41% cognitively declined, 15% improved, and 19% fluctuated over 36 months. Eighteen per cent of participants reverted to normal cognition from PD-MCI (Lawson et al., 2017). In PD and PDD different types of cognitive profiles and dementia have been described; in MCI a subcortical profile with attentional and executive dysfunction, and cortical cognitive impairment in memory and language as well as a mixed group are described (Janvin et al., 2003; Janvin et al., 2006). However, in PDD most cognitive domains are impaired, typically attention, executive functions, and visuospatial functions, but Goetz and colleagues (2008) found memory or language impairment in some patients.

Cognitive fluctuations

Fluctuations in DLB commonly occur in cognition, attention and level of arousal and can mimic delirium, with some patients changing rapidly from normal alertness and cognition through to sleepiness and confusion. Cognitive fluctuation is one of the core features of DLB and occurs in 25–50% of cases (Farina et al., 2009; Savica et al., 2013), depending of method of detection and disease stage. However, inter-rater reliability is

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low for clinical judgment of fluctuations, and standardized instruments should be applied (Ferman et al., 2004; Walker et al., 2000). The Mayo Fluctuations Composite Scale consists of four questions posed by the clinician to a caregiver regarding daytime drowsiness and lethargy, daytime sleep of two or more hours, staring into space for long periods, and episodes of disorganized speech. The scale has been validated in cognitively normal elderly, AD, and DLB, and fluctuations are present if three or four of the answers are 'yes'. Informed consent and decision-making from persons diagnosed with DLB should, ideally, therefore, be made in the most attentive phase (Spotorno et al., 2017).

Neuropsychiatric symptom profile

In addition to the visual hallucinations, delusions, and misidentification syndromes, apathy, depression, anxiety, and auditory hallucinations are common in DLB (Ricci et al., 2009). In PD, impulse control disorders like pathological gambling, hyper-sexuality, and compulsive buying have been described and found to be associated with dopamine-agonist treatment (Weintraub et al., 2010), but these symptoms have rarely been explored in DLB. Somatoform disorder, defined as medically unexplained symptoms, was found to occur in 7% of patients with PD and 12% of DLB patients preceding the DLB diagnosis for six months to ten years in all cases (Onofrj et al., 2010). Personality traits like diminished emotional responsiveness may distinguish DLB from AD (Galvin et al., 2007). Neuropsychiatric and behavioural symptoms are also very common in PDD, and were found in 89% in one study; symptoms most frequently reported were depression (58%), apathy (54%), anxiety (49%), and hallucinations (44%) (Aarsland et al., 2007).

Sleep disturbances in dementia with Lewy bodies and Parkinson's disease dementia

In DLB, as noted previously, RBD has been included as a core clinical feature in the clinical diagnostic criteria and hypersomnia or ED is included as a supportive clinical feature (McKeith et al., 2017). Up to 80% of patients with mild DLB or PDD have sleep disturbances, as compared to 56% of age-matched, cognitively normal controls and 64% of patients diagnosed with mild AD. The most common symptoms are insomnia (47%), sleep-related leg cramps (42%), EDS (41%), RBD (39%), restless legs syndrome (31%), obstructive sleep apnoea (26%), and periodic leg movements during sleep (21%) (Chwyszczuk et al., 2016; Rongve et al., 2010a). The Mayo sleep questionnaire has been validated to detect RBD in a dementia population (Boeve et al., 2013).

In PD, a wide range of different sleep disturbances have been described including insomnia, EDS, sleep attacks or unintended sleep episodes, RBD, restless legs syndrome, sleep-related leg cramps, periodic leg movements during sleep, obstructive sleep apnoea, and somnambulism (Jauregui-Barrutia et al., 2010; Mondragon-Rezola et al., 2010).

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Sleep disturbances in dementia have been thought to relate to pathology in specific brain areas such as the suprachiasmatic nucleus, the hypothalamus and brainstem, and pons area. Neurochemical changes affecting melatonin and acetylcholine have been reported with the profile of change contingent upon the specific brain pathology (Claassen et al., 2010).

Motor symptoms in dementia with Lewy bodies

The classical Parkinson symptoms such as resting tremor, bradykinesia, rigidity, and postural changes also occur in DLB, but symptoms are usually bilateral and postural instability, gait disorder, and rigidity usually dominate (Burn et al., 2006). In the 2017 diagnostic criteria, one or more symptoms of motor parkinsonism; bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity is sufficient for the core criterion to be fulfilled. Neuroleptic medication can cause or severely worsen parkinsonism and other motor disability in dementia, particularly in DLB and PDD (Aarsland et al., 2005a). Of note, in elderly people musculoskeletal problems are common and can lead to motor problems as well; the presence of these can compound the impact of any parkinsonism that is present. Repeated falls are one of the supportive clinical features for diagnosing DLB.

Autonomic failure in dementia with Lewy bodies and Parkinson's disease dementia

Autonomic failure can be an early and prominent feature of DLB and PDD as a consequence of involvement of the sympathetic ganglia and peripheral nervous system. Symptoms of autonomic failure are more common in DLB than in AD and include orthostatic hypotension, cardiac arrhythmias, syncope, constipation, impotence, urinary retention, and excessive sweating (Allan et al., 2007; Sonnesyn et al., 2009).

Clinical differential diagnosis

DLB and AD can be difficult to reliably differentiate clinically. The clinical diagnosis of dementia is based on an interview with both the person with dementia and the caregiver, and an active approach to the core and suggestive clinical features is important to detect DLB. In addition to a clinical examination, which includes physical and neurological examination and cognitive testing, other supplemental tests include blood work-up and magnetic resonance imaging (MRI), and CSF analysis to exclude other intracranial pathology is indicated. Although MRI and CSF can support a diagnosis of AD, these techniques cannot reliably distinguish between AD and DLB. Of note, both ^{123}I -FP-CIT SPECT and MIBG myocardial scintigraphy have been shown to have high sensitivity and specificity to differentiate between probable DLB and non-DLB dementia (see Biomarkers) and thus should be considered particularly where the diagnosis is less clear. A cognitive profile with executive and

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visuospatial impairment and preserved memory and language may raise the suspicion of DLB.

As per the consensus criteria, DLB is differentiated from PDD based on the one-year rule, i.e. in DLB parkinsonian motor symptoms can start up to one year before the dementia syndrome. If motor parkinsonian symptoms start more than one year before dementia the condition is diagnosed as PDD. Whether this is a biologically valid distinction, or whether PDD and DLB are merely syndromes on a continuum of Lewy body disease, is not known. Currently, unlike the distinction between DLB and AD, there are no major prognostic or therapeutic consequences related to the distinction between PDD and DLB.

Vascular dementia and frontotemporal dementia (FTD) can, in most cases, be differentiated from DLB based on the clinical interview and examination and supplemental tests like MRI and perfusion SPECT. However, progressive supranuclear palsy (PSP), multisystem atrophy, corticobasal degeneration, and FTD can be difficult to differentiate from DLB and PDD on the basis of ^{123}I - FP- CIT SPECT alone as these conditions can present with parkinsonism, reduced uptake on ^{123}I - FP- CIT SPECT and cognitive impairment (McKeith et al., 2017). MRI can assist in identifying vascular parkinsonism. PSP is a tauopathy and characterized by axial parkinsonism, early tendency to fall backwards, and impaired vertical eye movements. PSP can be complicated by subcortical dementia and must be differentiated from other tauopathies like the FTDs. Corticobasal degeneration has tau pathology and is characterized by more severe motor impairment with apraxia, agnosia, parkinsonism, aphasia, and alien hand syndrome with poor response to L-dopa and. Multiple system atrophy (MSA), an α -synucleinopathy, is characterized clinically by the early development of ataxia, autonomic failure, and symmetrical parkinsonism with rigidity and bradykinesia without tremor. Patients have poor response to L-dopa treatment and poor prognosis. MRI can in many cases inform the clinical diagnosis. In frail, elderly people symptoms like parkinsonism and impaired cognition can be caused by neuroleptic medication and thus a drug history must be taken during the diagnostic process. A ^{123}I - FP- CIT SPECT can be used to differentiate brain-stem parkinsonism from other motor impairments, e.g. drug-induced parkinsonism, essential tremor, and vascular parkinsonism (Contrafatto et al., 2011; Vlaar et al., 2008).

Another potential differential is posterior cortical atrophy (PCA) is increasingly recognized as a new clinical subtype of dementia and can include visual symptoms that might resemble DLB.

Pharmacological treatment for Parkinson's disease dementia and dementia with Lewy bodies

The pharmacological treatment for DLB is challenging due to high sensitivity to side effects and the risk of improving one symptom and simultaneously worsen other symptoms. Treatment is still symptomatic as

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no disease-modifying therapy is yet available. Identifying and prioritizing target symptoms and applying evidence-based measures with careful dosing and monitoring schedules is important for the comprehensive management of the disease (Aarsland et al., 2017; Velayudhan et al., 2017). Three meta-analyses, including 17 randomized and controlled studies, have found both rivastigmine and donepezil to be superior to placebo in improving cognition, behavioural disturbances, global functioning, and ADL-function with no worsening in motor functioning (Matsunaga et al., 2016; Stinton et al., 2015; Wang et al., 2014). Donepezil has been proven effective for up to 52 weeks regarding cognition and neuropsychiatric symptoms in DLB (Ikeda et al., 2013). Studies have suggested that memantine is a safe and potentially effective treatment for DLB and PDD, although findings have been inconsistent with significant improvement on a global measure and in neuropsychiatric symptoms in DLB only (Emre et al., 2010), although in a smaller study Aarsland and colleagues (2009a) indicated improvement also in PDD. Sleep (Aarsland et al., 2009a) and quality of life (Larsson et al., 2011) were shown to improve with memantine in another clinical trial, and in a meta-analysis Stubendorff and colleagues (2014) found memantine to improve DLB globally.

L-dopa is the main treatment of motor symptoms in PD and has been shown to improve parkinsonian symptoms in DLB in open-label studies, but side effects such as hallucinations and orthostatic hypotension can occur (Molloy et al., 2005). L-dopa has a complex and state-dependent effect on cognition in PD, and can improve some cognitive symptoms in some patients (MacDonald et al., 2011).

Treating psychotic symptoms in DLB is complicated and these patients often should be treated for psychosis in specialist settings. Nonpharmacological interventions like improving eye sight, exposure to light, and general activation (e.g. with social engagement) is recommended alongside reducing dopaminergic medications if possible. As a next step starting cholinesterase inhibitors (ChEIs) is recommended to reduce psychotic symptoms. Pimavanserin, a selective serotonin 5-HT_{2A} inverse agonist, is effective at doses of 40mg per day at reducing psychotic symptoms in PD (Cummings et al., 2014), but has not been studied in DLB and is only licensed for use in PD psychosis in a limited number of countries. In a sub-study of the effect of Pimavanserin in PD, a particular pronounced antipsychotic effect was noted in those with the most impaired cognition (Ffytche et al., 2017). Clozapine has been found to have a convincing effect on psychotic symptoms in PD, and this benefit may extend to include patients with cognitive impairment (Rongve et al., 2012). Although some open-label reports suggest that atypical antipsychotics such as quetiapine and clozapine may be useful for psychosis in PD or DLB (Poewe, 2005), the two randomized controlled trials in DLB reported either no effect of quetiapine on agitation and psychosis (Kurlan et al., 2007) or worsening of psychiatric symptoms from risperidone and citalopram (Culo et al., 2010). Antipsychotic medications

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have been found to significantly increase the risk of cerebral haemorrhages and infarctions, pneumonia, and death in elderly people with dementia (Ballard et al., 2009) and in both DLB and PDD neuroleptic hypersensitivity is much more common than in AD (Aarsland et al., 2005a). We therefore advise to administer antipsychotic medication for this group of patients only if psychotic symptoms are severe and persistent, and preferably in a specialist setting with close monitoring of the patient.

In PD antidepressants such as nortriptyline, paroxetine, and venlafaxine and also the dopamine agonist pramipexole have demonstrated antidepressant effect compared to placebo, but unfortunately no randomized controlled trials for treating depression have been carried out in DLB or PDD (Seppi et al., 2011).

Autonomic failure can be treated symptomatically, i.e. orthostatic hypotension can be improved by reducing or omitting drugs with orthostatic hypotension as a known side effect, anti-hypertensive drugs, and ensuring an adequate intake of fluids. Standard laxatives can be used to treat constipation; anticholinergic agents are used to treat bladder dysfunction but should be used with caution, particularly in elderly patients who have cognitive decline and dementia, and in particular DLB or PDD. Phosphodiesterase inhibitors can be used to treat sexual dysfunction (Zesiewicz et al., 2010).

RBD can be treated using clonazepam, melatonin, ChEI, or pramipexole (Aurora et al., 2010). Hypersomnia has been shown to improve with armodafinil in a pilot study (Lapid et al., 2017).

Disease-modifying approaches are aimed at preventing, slowing, or ameliorating the production, aggregation, and deposition of pathological proteins, including immunotherapy targeting α -synuclein and, at time of writing, an ongoing trial using amroxol, which increases glucocerebrosidase activity to lower the levels of the protein α -synuclein. Nilotinib, a protein tyrosine kinase inhibitor, was found safe for treating motor and cognitive symptoms in advanced PD and DLB in a phase one study (Pagan et al., 2016), and phase two studies are ongoing at the time of writing. Other disease-modifying clinical trials are using agents to augment insulin signalling, stem cell therapy, reducing amyloid pathology, and gene therapy (Velayudhan et al., 2017).

Nonpharmacological treatment of dementia with Lewy bodies and Parkinson's disease dementia

Two systematic reviews on different types of nonpharmacological interventions in PDD and DLB have been published recently, and while the studies included mostly report the intervention to be effective, direct comparisons and meta-analyses are difficult due to the many small and methodologically different studies (Connors et al., 2018; Morrin et al., 2018). General principles regarding nonpharmacological interventions in dementia apply also in DLB and PDD. In PD, some improvement in

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cognitive tests has been reported after cognitive training in randomized trials (Paris et al., 2011; Peña et al., 2014) and improvements have been found in PD when combining cognitive training with gait training and in a study which used an integrative cognitive rehabilitation program (Díez-Cirarda et al., 2017; Strouwen et al., 2017). Transcranial direct cortical stimulation (tDCS) has been studied in DLB and PDD and found to be tolerated and potentially beneficial to increase attention and mood and improve motor symptoms in a small open and controlled study (Elder et al., 2016), but no effect was found with larger controlled study on cognition (Elder et al., 2017). Similar it has no effect on visual hallucinations (Elder et al., 2019) or mood in a larger controlled study in PD (Brys et al., 2016). It is important to inform patients and caregivers regarding the characteristic features of DLB including the potentially harmful effects of RBD and neuroleptics. Most authors recommend identifying one or only a few target symptoms to deal with first. Online support groups for carers and information for carers, patients, and professionals are available at <http://lbda.org/> or <http://www.lewybody.org/>, <http://www.parkinsons.org.uk/>, and at the DIAMOND-Lewy research programme: <https://research.ncl.ac.uk/diamondlewy/>

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Frontotemporal dementia

Chapter: Frontotemporal dementia

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Development and evolution of frontotemporal dementia concepts

The term ‘frontotemporal dementia’ (FTD) has evolved significantly since 1892, when Arnold Pick first described a 71-year-old male patient with a progressive speech disorder, reported as ‘transcortical sensory aphasia’ (Pick, 1892). Post-mortem examination confirmed focal cerebral atrophy, mainly in the left superior temporal gyrus. The histopathological presence of argyrophilic globular neuronal cytoplasmic inclusions (later termed Pick bodies) was subsequently described by Alois Alzheimer (1911). As a result, the concept of Pick’s disease (PiD) as a clinicopathological entity was introduced in the early 1920s (Gans, 1925; Onari and Spatz, 1926).

In the following decades, the clinical and neuropathological heterogeneity of cases with atrophy in the frontal and/or temporal lobe became apparent, with evidence that Pick’s pathology was present in only around 20% of clinical FTD cases (Escourolle, 1958). Multiple other pathologies

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were subsequently associated with this focal dementia presentation (Brun, 1987; Mann et al., 1993), culminating in the Lund and Manchester (1994) groups description of a set of clinical and neuropathological criteria for FTD in 1994. These were updated in 1998 with the 'Neary criteria', when the term 'frontotemporal lobar degeneration' (FTLD) was introduced to describe the group of neurodegenerative diseases characterized by selective frontal and/or temporal lobe atrophy and non-Alzheimer's disease neuropathology (Neary et al., 1998).

Clinically, it was recognized that patients with frontotemporal atrophy developed personality change and/or language impairment. The majority of early studies had focused on those with changes in behaviour and personality, and the term Pick's disease became synonymous with this condition. Few studies investigated progressive language disorders until the last quarter of the twentieth century when two parallel streams of research started to describe such cases: Warrington (1975) described a group of patients with selective impairment of semantic memory, subsequently called 'semantic dementia' (SD) (Hodges et al., 1992), and Mesulam (1982, 1987) described people who had developed a 'primary progressive aphasia' (PPA).

The 'Neary criteria' (1998) provided diagnostic descriptions for both the behavioural and language variants, with the language impairment group divided into two separate syndromes: progressive non-fluent aphasia (PNFA) and SD. Although Mesulam (1987) and McKhann and colleagues (2001) independently described other criteria around the same time, the 'Neary criteria' provided the main research and clinical descriptions of these conditions until the last few years.

An international consortium of FTD researchers came together at the end of the first decade of the twenty-first century to revise the criteria for both the behavioural and language variants. The 'Rascovsky criteria' (Rascovsky et al., 2011) introduced the term behavioural variant (bvFTD), and the 'Gorno-Tempini criteria' (Gorno-Tempini et al., 2011) brought together work from various studies showing that there were more than two forms of PPA—these criteria describe three: a non-fluent or agrammatic variant (nfvPPA), a semantic variant (svPPA), and a logopenic variant (lvPPA), also called logopenic aphasia (LPA). While there is general consensus over the naming of bvFTD, there remains some disagreement over the nosology of PPA; PNFA/nfvPPA, SD/svPPA, and LPA/lvPPA are often used interchangeably, with the recognition that there are a sizeable minority of cases that do not fit criteria for any of the three subtypes (Harris et al., 2013).

Neither the Rascovsky nor the Gorno-Tempini diagnostic criteria describe the overlap of FTD with motor disorders. Around 15% of patients with FTD develop motor neurone disease (MND; Jackson et al., 1996) or amyotrophic lateral sclerosis (ALS), and a separate set of criteria have been developed by Strong (Strong et al., 2009, 2017) to describe any form of cognitive or behavioural change that occurs in MND/ALS. Individual

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diagnostic criteria also exist for the atypical parkinsonian disorders, corticobasal syndrome (CBS), and progressive supranuclear palsy (PSP)—the most recent criteria mention the possibility of the development of behavioural and language problems in these conditions (Armstrong et al., 2013; Hoglinger et al., 2017).

Epidemiology and life expectancy survival

Typical onset of FTD is between 45 and 65 years of age but there is a wide range from the early twenties through to the nineties (Rascovsky et al., 2011; Coyle-Gilchrist et al., 2016). There have been very few epidemiological studies of FTD (Onyike and Diehl-Schmid, 2013) but in the 45–65 age group, the estimated prevalence has been calculated as 15–22/100,000, with an incidence of 2.7–4.1/100,000, and an equal gender distribution. However, a recent study that incorporated all of the FTD spectrum disorders (including CBS and PSP) suggested an overall all age prevalence of 10.8/100,000 and incidence of 1.6/100,000, and an estimated lifetime risk of 1 in 742 (Coyle-Gilchrist et al., 2016).

Currently, the only confirmed risk factors for FTD are mutations in specific genes (see Genetics). Clear non-genetic risk factors are yet to be identified: a Dutch retrospective study found that head trauma was associated with a 3.3-fold higher risk for FTD, and thyroid disease with a 2.5-fold higher risk (Rosso et al., 2003a,b), but these have not been replicated yet in other studies, although more recently, one group has found a higher incidence of autoimmune diseases in a subgroup of patients with FTD (Miller et al., 2016).

Survival varies widely, ranging from 1–20+ years, and is dependent on the underlying clinical, genetic, and pathological cause (Onyike and Diehl-Schmid, 2013): clinically, svPPA has the longest median survival (12 years), nfvPPA and bvFTD show comparable survival (9 years) (Nunnemann et al., 2011; Roberson et al., 2005), while FTD-MND has the poorest prognosis with average time to death from symptom onset being between two and three years (Hodges et al., 2003). However, there is variability within each group, and a slowly progressive form has been described with survival >20 years, in some cases in association with an expansion in the *C9orf72* gene.

Genetics

A family history of dementia is found in about a third to a half of cases of FTD (Gräsbeck et al., 2005), but a true autosomal-dominant disorder is only found in 20–30% (Goldman et al., 2005; Rohrer and Warren, 2011; Rohrer et al., 2009b). Mutations in three genes account for more than 80% of genetic FTD: microtubule-associated protein tau (*MAPT*) (Hutton et al., 1998), progranulin (*GRN*) (Baker et al., 2006; Cruts et al., 2006), and chromosome 9 open reading frame 72 (*C9orf72*), (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Many other rare genetic causes for FTD have been described in a small number of families worldwide (Table 33.1).

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Table 33.1 Genetic causes of FTD.			
Gene		Year of discovery	Reference
<i>MAPT</i>	Microtubule-associated protein tau	1998	Hutton et al., 1998; Spillantini et al., 1998; Poorkaj et al., 1998
<i>VCP</i>	Valosin-containing protein	2004	Watts et al., 2004
<i>CHMP2B</i>	Chromatin-modifying protein 2B	2005	Skibinski et al., 2005
<i>DCTN1</i>	Dynactin-1	2005	Münch et al., 2005
<i>GRN</i>	Progranulin	2006	Baker et al., 2006; Cruts et al., 2006
<i>TARDP</i>	Transactive response DNA-binding protein-43	2008	Sreedharan et al., 2008
<i>FUS</i>	Fused in sarcoma	2009	Kwiatkowski et al., 2009
<i>C9ORF72</i>	Chromosome 9 open reading frame 72	2011	DeJesus-Hernandez et al., 2011; Renton et al., 2011
<i>SQSTM1</i>	p62/sequestome1	2012	Rubino et al., 2012
<i>UBQLN2</i>	Ubiquilin 2	2013	Gellera et al., 2013
<i>CHCHD10</i>	Coiled-coil-helix-coiled-coil-helix domain containing 10	2014	Bannwarth et al., 2014

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<i>TBK1</i>	TANK-binding kinase 1	2015	Freischmidt et al., 2015; Pottier et al., 2015
<i>CCNF</i>	Cyclin F	2016	Williams et al., 2016
<i>TIA1</i>	T cell-restricted intracellular antigen-1	2017	Mackenzie et al., 2017

Few genetic modifiers of FTD have been described, although two GWAS studies have been performed in FTD (van Deerlin et al., 2010; Ferrari et al., 2014). The first study focused only on those with TDP-43 pathology (see Neuropathology) and found that variants in the transmembrane protein 106B (*TMEM106B*) gene were a risk factor for FTD in that cohort, particularly in those with *GRN* mutations (Lattante et al., 2014; van Deerlin et al., 2010). The second GWAS study was in an unselected FTD cohort and therefore heterogeneous containing patients with multiple different pathologies. Nonetheless, two novel associations were found, with an *HLA* locus and with a locus at 11q14, encompassing *RAB38/CTSC*.

Among the clinical syndromes, bvFTD is most frequently associated with a genetic cause, followed by FTD-MND, nfvPPA, CBS, PSP, and lastly svPPA, which is usually sporadic (Rohrer et al., 2009a). *MAPT* gene mutations are typically associated with bvFTD and they account for virtually all hereditary tau-positive FTD. *GRN* mutations are most commonly associated with bvFTD, but nfvPPA can also be seen as can CBS. *C9orf72* expansions are found in patients with bvFTD, FTD-MND (or pure MND), and less commonly nfvPPA.

Neuropathology

The term FTLT is now most commonly used to describe the pathological forms of FTD, with its subclassification based on the type of protein inclusions found (Fig. 33.1; Lashley et al., 2015). The main distinction is between FTLT-tau, accounting for about 45% cases and the tau-negative cases. FTLT-tau can be subdivided on the basis of the predominant tau species (characterized by the presence of three or four repeat sequences in the isoform) present in the inclusions: while the amount of 3R-tau and 4R-tau is equal in the normal brain, 3R-tau is the predominant form in Pick's disease (Delacourte et al., 1996) and in some forms of FTDP-17, i.e. in those with *MAPT* mutations (Ghetti et al., 2015) while 4R-tau is seen in corticobasal degeneration (CBD), PSP, argyrophilic grain disease (AGD), globular glial tauopathy (GGT), and in some FTDP-17 variants (Ghetti et al., 2015; Flament et al., 1991; Ksiezak-Reding et al., 1994; Tolnay et al., 2002). Some FTDP-17 *MAPT* variants show both 3R-tau and 4R-tau in the inclusions (Ghetti et al., 2015). Of the tau-negative FTD cases, the vast

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majority have inclusions of the nuclear protein TDP-43 (accounting for ~50% of all FTLD): based on the predominant lesion type and the distribution of the pathological inclusions, FTLD-TDP can be subdivided into four different subtypes: A, B, C, and D (Mackenzie et al., 2011).

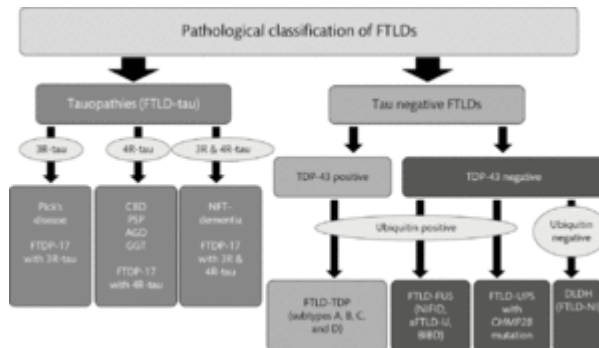


Fig. 33.1

A schematic illustration of the pathological classification of frontotemporal lobar degeneration. Current classification is based on the molecular features of the disease-associated, inclusion-forming proteins, morphological phenotypes and genetic data (for description of the different disease groups and individual diseases see text).

3R-tau, three-repeat tau; 4R-tau, four-repeat tau; aFTLD-U, atypical frontotemporal lobar degeneration with ubiquitin immunoreactive neuronal inclusions; AGD, argyrophilic grain disease; BIBD, basophilic inclusion body disease; CBD, corticobasal degeneration; DLDH, dementia lacking distinctive histology; FTLD, frontotemporal lobar degeneration; FTDP-17, frontotemporal dementia and parkinsonism linked to chromosome 17; GGT, globular glial tauopathy, NFT-dementia, neurofibrillary tangle dementia; NIFID, neuronal intermediate filament inclusion disease.

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Other pathologies are rare. Inclusions positive for the FUS protein (FTLD-FUS) account for ~5% of all FTLD (Mackenzie et al., 2010; Neumann et al., 2009a,b), and this group includes diseases such as neurofilament inclusion body disease (NIFID), atypical FTLD-U (aFTLD-U), and basophilic inclusions body disease (BIBD) (Neumann et al., 2009a,b; Urwin et al., 2010; Munoz et al., 2009). Patients with *CHMP2B* mutations are extremely rare (occurring mainly only in a single large Danish family)—these patients have ubiquitin-positive inclusions (FTLD-UPS) that are

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negative for tau, TDP-43, and FUS (MacKenzie et al., 2006; Seelaar et al., 2010).

bvFTD is the most heterogeneous of the clinical syndromes and it can be caused by any of the pathologies. svPPA is usually caused by FTLD-TDP type C, while nvPPA is associated with CBD, PSP, or Pick's disease (i.e. FTLD-tau) more commonly than FTLD-TDP (types A or B). A PSP clinical syndrome is predominantly associated with PSP pathology but CBS is only associated with CBD pathology in about 50% of cases, with other causes being PSP, Pick's disease, and FTLD-TDP type A. FTD-MND is generally associated with FTLD-TDP type B.

Genetic mutations in *MAPT* are associated with the FTDP-17 pathology, while the majority of the other genetic forms of FTD are associated with FTLD-TDP: *GRN* (type A), *C9orf72* (type A or B), *TBK1* (type A or B), *VCP* (type D). *C9orf72*, in addition to TDP-43 pathology, is characterized by neuronal inclusions composed of dipeptide repeat proteins (DPRs) in the cerebellar granule cell layer, hippocampal pyramidal neurons, and other neuroanatomical sites (Ash et al., 2013; Mori et al., 2013).

Clinical features

Behavioural variant FTD

bvFTD presents with an insidious onset of change in personality and behavioural symptoms. In the early stages these can be subtle and may be misdiagnosed as depression or a primary psychiatric illness. In the diagnostic criteria, symptoms fall into five main groups: disinhibition, apathy, changes in eating habits (gluttony, food fads, sweet food preference), obsessive-compulsive behaviour, and loss of empathy (Table 33.2). However, other changes of behaviour can be seen that do not form part of the criteria, including loss of insight, changes in pain and temperature sensitivity (Fletcher et al., 2015), and in a smaller number of patients delusions and/or hallucinations (commonly visual) (Woollacott and Rohrer, 2016).

Table 33.2 Summary of behavioural and cognitive symptoms within the current diagnostic criteria for behavioural variant frontotemporal dementia (bvFTD) and other commonly seen features.

Behavioural/cognitive symptoms - diagnosis of possible bvFTD requires at least three of the following symptoms to be fulfilled:	Examples of specific symptoms
Early behavioural disinhibition ≥ 1 of:	

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Socially inappropriate behaviour	Staring, inappropriate physical contact with strangers, inappropriate sexual behaviour, verbal or physical aggression
Loss of manners or decorum	Lack of social etiquette, insensitive or rude comments, preference for crass jokes and slapstick humour, inappropriate choices of clothing or gifts
Impulsive, rash or careless actions	New gambling behaviour, driving or investing recklessly, overspending, gullibility to phishing/Internet scams
Early apathy or inertia ≥ 1 of:	
Apathy	Reduced drive, stops previous hobbies, stops going out, reduced bathing or personal care
Inertia	Lack of persistence or completion of an activity, does not initiate activities or conversations
Early loss of sympathy or empathy ≥ 1 of:	
Diminished response to other people's needs and feelings	Selfish or hurtful comments or actions, inability to perceive when someone is upset, embarrassed, or in pain, reduced appreciation of sarcasm or sophisticated humor
Diminished social interest, interrelatedness, or personal warmth	Emotionally cold or detached, lack of rapport in conversation, loss of interest or affection in relationships with friends or family members, reduced interest in sex
Early perseverative, stereotyped or compulsive or ritualistic behaviour ≥ 1 of:	
Simple repetitive movements	Repetitive rocking, tapping, clapping, or rubbing

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Complex compulsive or ritualistic behaviours	Hoarding, strict grooming or walking routines, timekeeping and counting, checking or sorting items, cleaning or tidying, new obsessions or interests (usually spiritual, religious, artistic, or musical)
Stereotypy of speech	Habitual repetition of particular words, sentences, or topics
Hyperorality and dietary changes ≥ 1 of:	
Altered food preferences	Sweet tooth (sweets, biscuits, ice cream), carbohydrates, or obsessive food fads
Binge eating, increased consumption of alcohol or cigarettes	Cramming food into mouth, overeating or messy eating, new addictions to alcohol or smoking
Oral exploration or consumption of inedible objects	Pica
Neuropsychological profile - all 3 of:	
Deficits in executive tasks	Vary as per neuropsychological assessment used
Relative sparing of episodic memory	
Relative sparing of visuospatial skills	
Other features of bvFTD (not in diagnostic criteria)	
Loss of insight	Lack of awareness of own condition or symptoms
Impaired social cognition	Poor response to social or emotional clues; impaired performance on tests of theory of mind or emotion recognition

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Altered sensitivity to pain	Heightened perception of a non-painful stimulus or reduced response to painful stimulus; hypochondriasis or overly focusing on mild physical complaints
Altered tolerance of temperature	Inappropriate clothing for the ambient temperature, such as wearing multiple coats or blankets
Psychotic features	Delusions (usually somatic or paranoid) and hallucinations (usually visual or tactile)

Table content is adapted from Rascovsky et al. (2011) and Warren et al. (2013). To qualify for a diagnosis of possible bvFTD, patients need to have a progressive deterioration of behaviour and/or cognition as per observation or history from an informant, and must possess persistent evidence of least three of the six main groups of behavioural/cognitive symptoms as listed above. The term 'early' refers to within three years of initial symptom onset as per Rascovsky et al. (2011). Reproduced with permission from Woollacott, I.O., and Rohrer, J.D. The clinical spectrum of sporadic and familial forms of frontotemporal dementia. *J Neurochem.*, 138(S1):6–31. Copyright © 2016, International Society for Neurochemistry. <https://doi.org/10.1111/jnc.13654>.

Early cognitive impairment is usually in the domain of executive function, e.g. difficulties with decision-making, planning, and problem solving, and this also forms part of the diagnostic criteria. However, impairment of social cognition also commonly occurs in the early stages (Kumfor and Piguet, 2012), with many people arguing that the absence of this from the criteria is a major weakness. As the disease progresses other cognitive domains become involved, although there are a subset of patients that develop early episodic memory or parietal dysfunction.

Primary progressive aphasia

PPA is characterized by progressive and insidious language decline, affecting at least one of the following functions: speech production, object naming, syntax, and word comprehension (Gorno-Tempini et al., 2011). For the diagnosis of PPA, the deficits should not be caused by other non-degenerative disorders (e.g. tumour or stroke), initial symptoms should not include prominent behavioural or cognitive difficulties, and the symptoms should not be better accounted for by a psychiatric diagnosis. As noted earlier, within PPA, three main PPA variants are recognized: svPPA, nfvPPA, or lvPPA (Table 33.3; Gorno-Tempini et al., 2011), but a subgroup of patients who have PPA do not fit neatly into one of these three diagnoses, and have been called various names over the years,

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including a 'mixed aphasia', 'PPA-unclassified', or 'PPA-not otherwise specified' (Harris et al., 2013).

Table 33.3 Summary of clinical features across the syndromes of primary progressive aphasia.

Clinical features	svPPA	nvPPA	lvPPA
<i>Spontaneous speech (fluency, errors, grammar, prosody)</i>	Fluent, garrulous, and circumlocutory; semantic errors; intact grammar and prosody	Slow and hesitant, effortful +/- apraxic; phonetic errors; may be agrammatic; aprosodic	Hesitant; not effortful or apraxic; frequent word-finding pauses and loss of train of sentence; intact grammar; intact prosody
<i>Naming</i>	Severe anomia with semantic paraphasias	Moderate anomia with phonetic errors and phonemic paraphasias	Mild to moderate anomia with occasional phonemic paraphasias
<i>Single word comprehension</i>	Poor	Intact early on, but affected later on	Intact early on, but affected later on
<i>Sentence comprehension</i>	Initially preserved, later on becomes impaired as word comprehension is impaired	Impaired if grammatically complex	Impaired, especially if long
<i>Single word repetition</i>	Relatively intact	Mild to moderately impaired if polysyllabic,	Relatively intact (compared with

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		otherwise intact	sentence repetition)
<i>Sentence repetition</i>	Relatively intact	Can be effortful; impaired if grammatically complex	Impaired, with length effect
<i>Reading</i>	Surface dyslexia	Phonological dyslexia +/- phonetic errors on reading aloud	Phonological dyslexia
<i>Writing</i>	Surface dysgraphia	Phonological dysgraphia	Phonological dysgraphia

Clinical features are adapted from tables in Rohrer et al. (2008); Rohrer et al., 2010a; Seelaar et al. (2011); and Gorno-Tempini et al. (2011). Reproduced with permission from Woollacott, I.O., and Rohrer, J.D. The clinical spectrum of sporadic and familial forms of frontotemporal dementia. *J Neurochem.*, 138(S1):6–31. Copyright © 2016, International Society for Neurochemistry. <https://doi.org/10.1111/jnc.13654>.

Patients with svPPA present with anomia and impaired single word comprehension, and then later nonverbal semantic impairment as well. Speech is fluent, with frequent circumlocutions and semantic paraphasias. Speech articulation, prosody, and repetition of spoken words are usually preserved, and grammar is intact (Gorno-Tempini et al., 2011).

In comparison, patients with nfvPPA develop agrammatism and/or apraxia of speech, with phonemic and phonetic errors. Speech is non-fluent and the prosody of speech is disrupted, while single word comprehension, object knowledge, and repetition of single words are preserved (Gorno-Tempini et al., 2011). There is ongoing controversy over whether nfvPPA consists of more than one syndrome. For example, there is a parallel literature on patients who have a pure progressive apraxia of speech (PAOS) (Botha et al., 2015), i.e. have impaired planning of articulation but no language deficits per se. PAOS is then distinguished from those with progressive agrammatic aphasia who have syntax problems but no articulatory deficits. While nfvPPA remains undoubtedly heterogeneous, many patients have both apraxia of speech and agrammatism, making the distinction into two separate diseases difficult practically.

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lvPPA is characterized by word-finding pauses, anomia, phonemic errors, impaired sentence repetition, and impaired working memory. Single word comprehension and object knowledge are preserved, but there is impaired comprehension of longer sentences without agrammatism or apraxia of speech (Gorno-Tempini et al., 2011; Woollacott and Rohrer, 2016).

Motor disorders

Around 15% of people with FTD (usually bvFTD, or rarely nvfPPA) develop MND/ALS, although behavioural and/or cognitive impairment not meeting criteria for FTD is seen in around 50% of people with MND/ALS. Early features commonly include fasciculations and brisk reflexes.

Parkinsonian syndromes are seen most commonly in people with bvFTD or nvfPPA (and almost never in people with svPPA or lvPPA). While the majority of patients meet criteria for one of the atypical parkinsonian syndromes, PSP or CBS, there are a subgroup of people with (usually asymmetrical) parkinsonism who do not meet criteria for any of the defined parkinsonian disorders.

Summary of genetics, neuropathology, and clinical features

Fig. 33.2 summarizes the clinical syndromes, pathology and genetics of the FTD disorders, and shows (as discussed earlier) there are no one-to-one correlations between clinical syndrome and pathology, although a PSP syndrome (with PSP pathology), svPPA (with FTLD-TDP type C), and FTD-MND/ALS (with FTLD-TDP type B) have the strongest associations.

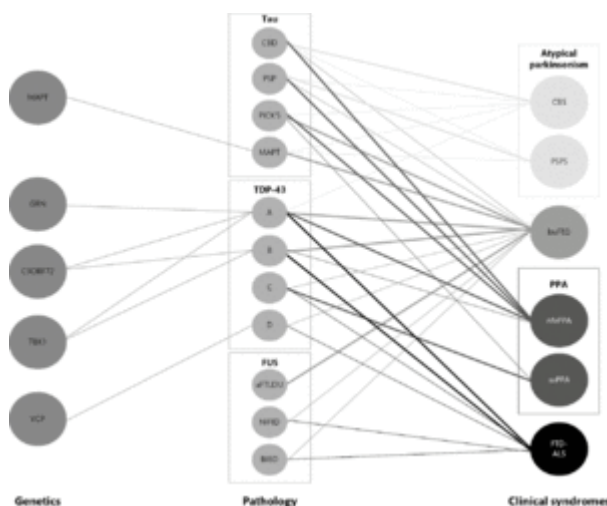


Fig. 33.2

Association between clinical syndromes, pathology, and genetics of the FTD spectrum disorders. Thicker lines linking clinical syndromes to pathology represent stronger associations. PSPS refers to a clinical syndrome of classical PSP, sometimes called Richardson's syndrome.

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Neuroimaging

FTD has been always described as a disease with a frontal and temporal lobe atrophic pattern (hence its name), which is clearly visible as volume loss on T1-weighted magnetic resonance imaging (MRI), and as areas of hypometabolism on ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET). However, it is clear that cortical atrophy is also present in the insula and anterior cingulate (in particular) as well as, on occasion, more posterior cortical structures. Furthermore, recent studies have shown that subcortical structures such as the hippocampus, amygdala, striatum, thalamus, and cerebellum can be affected even in the earliest stages of the disorder (Rohrer and Rosen, 2013; Whitwell et al., 2012; Seeley et al., 2008; Schroeter et al., 2007; Halabi et al., 2013).

In bvFTD, the atrophy pattern is often asymmetrical, affecting the right hemisphere more than the left (Rohrer and Rosen, 2013). However, this is not the case for all individuals, and at least four anatomical subtypes of bvFTD have been postulated: focal frontal- and temporal-dominant subtypes, as well as combined frontal/temporal and more widespread temporo-frontal-parietal subtypes (Whitwell et al., 2009).

svPPA is associated with a characteristic pattern of asymmetrical (usually left greater than right) atrophy of the temporal lobes, particularly the inferior temporal and fusiform gyri, the temporal pole, the parahippocampal and the entorhinal cortex, the anterior hippocampus, and the amygdala (Rohrer and Rosen, 2013; Gordon et al., 2016; Rohrer et al., 2009b; Schroeter et al., 2007). Less frequently, patients present with predominant right temporal lobe atrophy at onset, a condition often called right temporal lobe atrophy (RTLA) (Chan et al., 2009).

nvPPA patients typically show atrophy of the inferior frontal gyrus (particularly the pars opercularis), dorsolateral prefrontal cortex, superior temporal gyrus, and insula (Rohrer et al., 2009b), with involvement of the caudate and putamen (Gorno-Tempini et al., 2004). In contrast, lvPPA shows left temporoparietal atrophy, encompassing the posterior superior temporal lobe and inferior parietal lobe, as well as the precuneus, posterior cingulate, and medial temporal lobe (Gorno-Tempini et al., 2004; Rohrer, Caso et al., 2013).

The genetic forms of FTD appear to have a differential involvement of the cortical and subcortical areas (Fig. 33.3): patients with *MAPT* mutations present with focal symmetric anterior temporal and orbitofrontal lobe atrophy, with hippocampus and amygdala atrophy. Patients with *GRN* mutations usually present with asymmetric atrophy of the temporal, inferior frontal, and inferior parietal lobes and of the striatum, whereas patients with *C9orf72* expansions show a more distributed symmetric pattern of atrophy, predominantly involving dorsolateral and medial frontal and orbitofrontal lobes, with additional loss in the anterior temporal, parietal, and occipital lobes, as well as in the thalamus and

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cerebellum (Rohrer et al., 2010b, 2015; Whitwell et al., 2012; Sha et al., 2012).

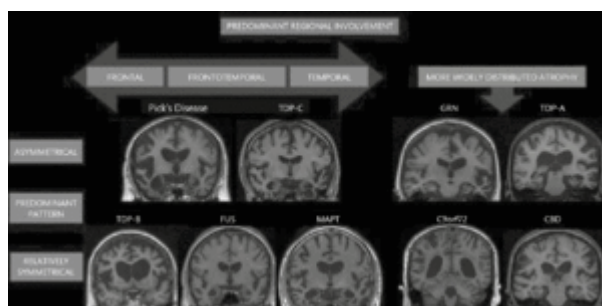


Fig. 33.3

Coronal T1 volumetric MR images displaying characteristic patterns and distribution of regional volume loss for each of the main genetic and pathological subtypes of FTD.

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Some studies have started to show specific imaging features in pathological subtypes of FTLTD (Fig. 33.3), e.g. PiD can be associated with asymmetric atrophy in the frontal, anterior temporal, and insula cortex, FTLTD-TDP type A with asymmetric fronto-temporo-parietal atrophy with anterior cingulate and caudate involvement, FTLTD-TDP type B with symmetrical frontal, insular, and anteromedial temporal lobe atrophy, FTLTD-TDP type C with asymmetrical loss in the antero-inferior temporal lobe, and FUS pathology with caudate, orbitofrontal, anteromedial temporal, anterior cingulate, and insula atrophy (Gordon et al., 2016; Seelar et al., 2010; Josephs et al., 2010).

Hypometabolism measured with FDG-PET and SPECT is commonly found in FTD, with similar patterns of neuroanatomical involvement to those seen with T1 MRI imaging (Diehl-Schmid et al., 2007). However, there have been fewer studies of these imaging modalities compared with MRI, in particular within genetic or pathological subtypes of FTD. Newer imaging techniques, e.g. arterial spin labelling (ASL), offer the opportunity of potentially measuring similar abnormalities as part of an MRI protocol (e.g. hypoperfusion in ASL; Hu et al., 2010) while not requiring injection of a radioactive ligand.

Initial studies using diffusion tensor imaging (DTI) and resting state functional magnetic resonance imaging (rs-fMRI) have started to highlight the involvement of structural and functional networks in FTD. Structurally, multiple white matter tracts have been identified as abnormal in FTD, e.g. the superior longitudinal, inferior longitudinal, and

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uncinate fasciculi (Mahoney et al., 2014; Lee et al., 2016; Dopper et al., 2013), while functionally, the key networks involved have been shown to be the salience and executive control networks in bvFTD and the language and semantic networks (predominantly in the left hemisphere) in PPA (Seeley et al., 2009; Lee et al., 2014; Pievani et al., 2014).

Amyloid-PET imaging (using tracers such as PIB or florbetapir) has demonstrated utility in FTD and PPA clinical syndromes in differentiating those people with underlying AD pathology (commonly lvPPA, and only rarely the other syndromes) from those with FTLD pathology (Rabinovici et al., 2008). Several PET ligands selective for tau pathology (e.g. AV1451, PBB3) have been developed but none have so far been shown to selectively identify non-AD tauopathies, or differentiate them from the TDP-43 proteinopathies (Villemagne et al., 2015).

Fluid biomarkers

Multiple studies have been performed in order to identify biomarkers in cerebrospinal fluid (CSF) or blood that might improve differential diagnosis of FTD or track disease progression (Oeckl et al., 2015; Oeckl et al., 2016). Similar to amyloid PET imaging, core AD CSF biomarkers (levels of total-tau, phospho-tau, and $A\beta_{42}$) show diagnostic power in differentiating those people with underlying AD pathology from those with FTLD (Bian et al., 2008; Paraskevas et al., 2017). However, also similarly to PET, no markers have been found that can differentiate those with FTLD-tau from those with FTLD-TDP; while the ratio of phospho-tau/total-tau is lower in FTLD-TDP than in FTLD-tau, the sensitivity and specificity is poor.

A promising biomarker of disease progression is the level of neurofilament light chain (NfL), which can be measured in CSF and blood. NfL levels are 2.5–11-fold higher in patients with all FTD subtypes than in controls, and they are correlated with survival and rate of brain atrophy (Landqvist Waldö et al., 2013; Meeter et al., 2016a; Rohrer et al., 2016).

Serum and CSF levels of progranulin are reduced by 25–40% in carriers of *GRN* mutations with high sensitivity (96–100%) and specificity (93–100%), and are therefore considered diagnostic biomarkers of pathogenic *GRN* mutations (Ghidoni et al., 2012; Meeter et al., 2016b).

C9orf72 expansion carriers show elevated levels of glycine-proline-repeating protein, one of the DPR proteins, in the CSF (Gendron et al., 2017).

Recent studies have focused on other potential fluid biomarkers for FTD, such as CSF levels of pTDP-43 (Kuiperij et al., 2017), neurogranin (Janelidze et al., 2016), or inflammation-related proteins (Oeckl et al., 2015; Oeckl et al., 2016).

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Management and treatment

There are currently no therapies that can delay the onset or prevent the progression of FTD. There have also been few clinical trials of potential disease modifying therapies so far, although that is likely to change in forthcoming years.

There are also few pharmacological therapies with any proven symptomatic benefit in FTD (Tsai and Boxer, 2016). Trials of symptomatic AD therapies (cholinesterase inhibitors and memantine) in FTD have been negative, and there is in fact some evidence that these therapies may aggravate behavioural disturbance in bvFTD (Mendez et al., 2007). There is some evidence from small studies (not double-blind randomized control trials) that selective serotonin reuptake inhibitors may improve behaviour in bvFTD and a trial of such a medication is commonly attempted clinically. There is also no strong evidence base for the use of neuroleptic drugs in FTD, despite relatively common use for agitation and other behavioural symptoms, and the risk/benefit ratio remains unclear.

Patients with PPA can benefit from a review from a speech and language therapist with an interest in PPA. Augmentative and alternative communication strategies and devices can be of benefit in PPA, particularly in the early stages of the disease.

In the absence of adequate therapies for FTD, management is directed at building a support network through community mental health, psychological, and social services as well as both local and national support groups (e.g. the national FTD, PPA, and familial FTD support groups run by www.raredementiasupport.org in the UK). Day centres and respite care are important to relieve the burden on carers and families. Provision of accurate information is required (e.g. from websites such as www.ftdtalk.org) to allow patients, family members, and carers to understand a disease which is commonly poorly understood in the community due to its rarity.

For those with familial FTD, access to genetic services is important. This may include genetic counselling, pre-symptomatic genetic testing, and preimplantation genetic diagnosis for family members.

Future management of FTD will hopefully include quicker and more accurate diagnosis and improved prediction of the rate of progression. For familial FTD, the ability to identify the time at which people will develop symptoms will be hugely important for pre-symptomatic mutation carriers (Woollacott and Rohrer, 2016). Lastly, while there is hope that future trials of disease modifying therapies are successful, until that time, it is important that patients and family members are able to access and participate in research studies as easily as possible.

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Neurological dementias

Chapter: Neurological dementias

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Dementia with onset in old age is usually due to neurodegenerative disease. Alzheimer pathology is the commonest cause, followed by Lewy body changes and, more rarely, the range of pathologies associated with frontotemporal dementia (FTD). These neurodegenerative conditions, in which dementia is the dominant feature, are often referred to as the *primary* dementias and are covered separately in Chapter 30, Chapter 32, and Chapter 33. Unfortunately, despite decades of research, the primary dementias are currently incurable.

Less commonly, dementia can arise as a complication of general medical conditions: in such *secondary* dementias, cognitive impairment is typically accompanied by symptoms and signs in other organ systems. Most commonly the underlying pathology is vascular disease; vascular risk factors such as smoking, alcohol use, obesity, diabetes, hypertension, and hypercholesterolaemia are also all risk factors for dementia, and vascular cognitive impairment and vascular dementia are covered separately in Chapter 31. General medical conditions such as hypothyroidism and

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vitamin B₁₂ deficiency are often listed as causes of a secondary dementia and are included in screening because they are treatable. However, dementia due solely to such conditions is rare and they are probably better regarded as treatable comorbidities rather than 'causes' as such.

Alternatively, dementia may develop as just one facet of a more extensive neurological disorder. Such *neurological* dementias are much less common than primary or vascular dementia but important to recognize because their management and outcomes may be very different. Accurate diagnosis and appropriate treatment often require referral outside of old age psychiatry services, and this chapter focuses on a selection of neurological dementias where a neurological consultation is likely to be of value: idiopathic normal pressure hydrocephalus, Huntington's disease, multiple sclerosis, antibody-mediated encephalitis, and prion disease.

Idiopathic normal pressure hydrocephalus (INPH)

Overview

INPH is a disorder in which abnormal accumulation of cerebrospinal fluid (CSF) results in gait disturbance, urinary incontinence, and dementia. Clinicians are anxious not to miss the diagnosis as it is potentially treatable, and the possibility of INPH is not infrequently raised in neuroimaging reports. However, the disorder in its full form is uncommon, diagnosis is challenging, and treatment can be associated with significant complications.

Hydrocephalus is an umbrella term for the abnormal accumulation of CSF within the cranium, whether due to defective CSF production, flow, or absorption. The two main types are *obstructive hydrocephalus*, where there is a structural barrier to CSF flow through the ventricular system, and *communicating hydrocephalus*, where the defect is inadequate CSF absorption by the arachnoid granulations. Hydrocephalus secondary to overproduction of CSF is rare. Communicating hydrocephalus may in turn be classified as either *primary* or *secondary*. In secondary communicating hydrocephalus, the defect in CSF absorption is due to a well-established cause of damage to the arachnoid granulations, e.g. meningitis, subarachnoid haemorrhage, or significant head injury. In primary communicating hydrocephalus, no such cause is apparent.

In 1965, Adams and colleagues (1965) published a description of three patients with ventriculomegaly, gait disturbance, urinary incontinence, and dementia in whom symptoms were improved by the insertion of a ventricular shunt. All three patients had CSF opening pressures within the normal range, and in two of the three cases no secondary underlying cause for the hydrocephalus could be found. Subsequently, this scenario was termed 'idiopathic normal pressure hydrocephalus' (INPH), but the label may be misleading—intracranial pressure (ICP) in INPH is in fact on average slightly higher than normal, with slow pulses (0.33 to 3 cycles/min) of slightly increased pressure known as B waves, probably related to

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rhythmic changes in cerebral blood volume. For this reason, some authors prefer the alternative label 'idiopathic adult hydrocephalus syndrome'.

The pathophysiology of INPH is incompletely understood. CSF dynamics are disturbed, with a high resistance to CSF outflow, slightly raised intracranial pressure, increased B-waves, an increased aqueductal stroke volume, and ventriculomegaly. However, the underlying cause for this disturbance is unknown, as is the mechanism by which these CSF pressure abnormalities affect the brain and result in clinical symptoms. A leading theory is that the symptoms of INPH are due to a complex interaction between a disturbance of CSF dynamics and cerebrovascular small vessel disease, resulting in low-grade cerebral ischaemia of periventricular white matter (Momjian, Owler et al., 2004) and basal ganglia (Townley et al., 2018). Microdialysis studies show that CSF removal is associated with improvement in this periventricular ischaemia (Agren-Wilsson et al., 2005).

Epidemiology

There are no definitive figures for the incidence and prevalence of INPH. In a door-to-door community survey of two Bavarian villages, the population prevalence of INPH in people older than 65 years was 0.4% (Trenkwalder et al., 1995), while in three Japanese studies the prevalence varied from 0.5% to 2.9% depending on the definition used (Hiraoka et al., 2008; Tanaka et al., 2009; Iseki et al., 2009). A more recent Swedish community-based study of 1,238 individuals who underwent both CT scanning and clinical examination suggests that in older adults INPH could be more common than previously thought, with a prevalence of 0.2% in individuals aged 70–79 years but 5.9% in individuals aged 80 and above (Jaraj et al., 2014). However, only a minority of patients proceed to surgical treatment. In a survey of six Swedish neurosurgical centres, the number of shunt insertions performed for INPH was only 1–2/100,000 per year (Tisell et al., 2005), while in a retrospective survey of Mayo Clinic records the number was 1.2/100,000 per year (Klassen and Ahlskog, 2011). In summary, INPH is not a common cause of dementia in later life but may be more common than previously thought.

Clinical features

The diagnosis of INPH rests first on clinical suspicion. The cardinal feature is disturbance of balance and gait, which almost always precedes the development of other symptoms and worsens insidiously over months and years. Patients walk with a mildly broad-based, small-stepped gait, and locomotion is impaired to a degree out of all proportion to the examination findings on the couch: this is often termed a gait apraxia. Although minor extrapyramidal features may be found on examination, the presentation is quite distinct from that of idiopathic Parkinson's disease (PD). Cognitive impairment is present in most patients with INPH by the time of diagnosis, generally with a 'subcortical' pattern, including pronounced slowness of thought, difficulty in sustaining, dividing, and

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switching attention, and difficulties in planning. However, simple bedside screening tests are generally unable to discriminate between the profiles of cognitive impairment associated with INPH and AD. Finally, urinary urgency, frequency, and incontinence are common but non-specific features (Malm and Eklund, 2006).

Investigations

A CT or MRI brain scan should be performed in any patient with clinical features suggestive of INPH. The first aim of neuroimaging is to exclude any structural lesion causing obstructive hydrocephalus, and the second is to look for supporting evidence of INPH. Enlargement of the ventricles is the cardinal feature of INPH and is traditionally assessed by calculation of Evan's ratio (the ratio of the greatest width of the frontal horns of the lateral ventricles to the maximum internal width of the skull). An Evan's ratio greater than 0.3 suggests significant ventriculomegaly, but not all ventriculomegaly is due to INPH: in the Swedish study mentioned above, 20.7% of the population had an Evan's ratio > 0.3 (Jaraj et al., 2014). Thus, other features are also important: e.g. disproportionate widening of the temporal horns of the lateral ventricles or flattening of the cortical sulci superiorly. In patients where significant ventriculomegaly is accompanied by marked cortical atrophy or signs of extensive cerebrovascular disease, ventriculomegaly may simply represent loss of brain tissue rather than INPH.

If there is supporting evidence for INPH on neuroimaging, the next step is typically specialist referral to either neurology or neurosurgical services. Before proceeding to more invasive tests and a decision about surgery, it is important to exclude degenerative disorders such as PD, significant vascular disease, and common neurological disorders of old age, e.g. cervical spondylotic myelopathy, lumbar canal stenosis, and a polyneuropathy (Malm et al., 2013). Exclusion of these possibilities rests largely on clinical assessment, but occasionally spinal imaging or neurophysiology studies may be necessary. Any MRI of the brain should also be carefully examined to rule out subtle secondary causes of hydrocephalus such as aqueduct stenosis. Based on the combination of clinical features and imaging abnormalities, consensus clinical diagnostic criteria for possible and probable INPH have been proposed (Relkin et al., 2005; Mori et al., 2012).

If specialist assessment confirms probable INPH, and there is no contraindication to proceeding, the next step is to decide if surgery (the placement of a ventricular shunt) will be of benefit. This usually involves further invasive investigations, either to measure aspects of CSF dynamics directly or to simulate the result of a shunt by removing a volume of CSF. The most widely used investigation is probably the CSF tap test, where 40–50 ml of CSF is withdrawn by lumbar puncture, with assessment of gait and cognition before and afterwards. Unfortunately, while this test has a reasonable specificity and positive predictive value (i.e. a positive result is a good predictor of a response to shunting), it has

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a low sensitivity and negative predictive value (i.e. a negative result does not exclude a response to shunting). For this reason, some neurosurgical centres advocate a prolonged trial of CSF removal, usually involving the placement of a lumbar catheter and the steady drainage of approximately 10 ml of CSF per hour for up to 72 hours. There is certainly some evidence that external lumbar CSF drainage is more sensitive in predicting response to shunting than a simple tap test, but drainage has the drawback of requiring an inpatient stay and carries a risk of catheter-related complications, including infection.

Alternatively, CSF dynamics may be measured directly. Twenty-four-hour intracranial pressure monitoring often reveals abnormalities that indicate poor cerebral compliance, such as the presence of low-amplitude B waves (as mentioned in Overview). However, studies suggest that the presence or absence of B waves has a poor correlation with response to shunting. A more comprehensive assessment of CSF dynamics can be obtained by CSF infusion testing, in which saline is infused into the sub-arachnoid space through a lumbar puncture needle, while CSF pressure is continuously recorded via a second lumbar puncture needle placed at a different level. In most patients, the pressure rises constantly and then reaches a plateau. From the baseline pressure, plateau pressure, and infusion rate, the resistance to CSF absorption can be calculated. At present, CSF infusion measurements suffer from the same problem as drainage studies when it comes to predicting a response to shunting, namely a good specificity but poorer sensitivity. However, sophisticated analysis of the infusion data and refinements of the technique may improve its sensitivity in the future. Table 34.1 summarizes clinical factors and investigation results that may help predict the response to shunting.

Table 34.1 Factors associated with response or lack of response to shunting in INPH	
Factors associated with response to shunting	Factors associated with a lack of response to shunting
• Gait disturbance preceding cognitive impairment • Mild cognitive impairment, present for a short duration	• Cognitive impairment preceding gait disturbance • Moderate or severe cognitive impairment, present for two or more years
• Clinical improvement (usually in gait) following lumbar puncture or	MRI shows significant cerebral atrophy or white matter abnormalities

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continuous lumbar CSF drainage • Resistance to CSF outflow of 18 mmHg/ml per min or greater during continuous lumbar CSF infusion test • Presence of B waves more than 50% of the time during continuous lumbar CSF monitoring	

Treatment and outcome

The surgical treatment for INPH is placement of a ventriculoperitoneal (VP) shunt, consisting of a proximal shunt catheter inserted in one of the lateral ventricles, a valve to regulate CSF drainage, and a distal catheter discharging into the peritoneal cavity. Fig. **34.1** shows typical preoperative and postoperative CT scan appearances in INPH. Most shunt valves are differential pressure-regulated, with an opening pressure above which the valve opens to permit CSF drainage and below which it closes again. The dilemma is that while adequate drainage is needed to see any clinical benefit, overdrainage may lead to low pressure symptoms and the accumulation of subdural hygromas or haematomas: in an early Dutch trial, low opening pressure valves were associated with better clinical outcomes than medium-pressure valves but also a threefold higher relative risk of chronic subdural effusions (Boon et al., 1998). The development of adjustable pressure-regulated shunt valves has allowed a more nuanced approach (e.g. rather than setting a fixed, low opening pressure, the opening pressure can be set high initially and then adjusted downwards at intervals to either a predetermined level or until clinical benefit is seen), but there is no consensus as to the optimum approach. One Dutch study found an adjustable strategy was as effective as a fixed low-pressure strategy, with significantly fewer subdural effusions (Delwel et al., 2013), and one Norwegian study found an adjustable strategy was more effective but with the same rate of complications (Saehle et al., 2014), but a randomized double-blind trial found no difference in effectiveness or complication rates between the two approaches (Farahmand et al., 2016).

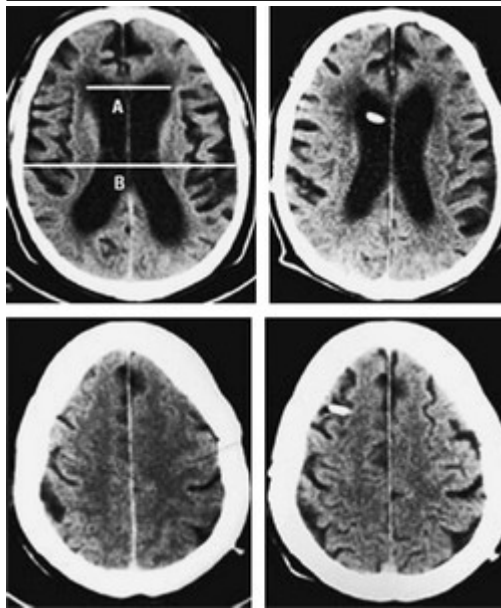


Fig. 34.1

Preoperative (left) and postoperative (right) axial CT brain scans in INPH. Preoperatively, the ventricles are widened (upper left) and the cortical sulci in the top slices are partially effaced (lower left). Evan's ratio, calculated as the ratio of the greatest width of the frontal horns of the lateral ventricles (A) to the maximal internal diameter of the skull (B), is approximately 0.4; a ratio more than 0.3 is significant. Postoperatively, observe the tip of the shunt catheter in the lateral ventricle (upper right) and traversing the brain parenchyma (lower right), with a reduction in ventricular size and widening of cortical sulci.

Reproduced with permission from Malm, J. and Eklund, A. Idiopathic normal pressure hydrocephalus. *Practical Neurology*, 6(1): 14-27. Copyright © 2006, *British Medical Journal*. <http://dx.doi.org/10.1136/jnnp.2006.088351>.

One reason for this variation in outcome with differential pressure-regulated shunt systems may be that the pressure differential changes with changes in posture. If the valve is programmed to provide adequate drainage with the patient supine, it may result in overdrainage when upright, leading to subdural collections. However, if the drainage is set with the patient standing, it may result in underdrainage when supine, reducing the effectiveness of shunt surgery. To overcome this effect, gravitational ball-in-cone units have been developed that switch between a low-pressure mode when supine and a high-pressure mode when upright: one open-label study suggested that this reduced the rate of shunt-related complications (Lemcke et al., 2013), but the different shunt systems have not been trialled against one another head to head. Flow-regulated (as opposed to pressure-regulated) valves are also available.

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The nature, magnitude, and duration of the benefit obtained by shunting is controversial. In non-placebo-controlled studies, up to two-thirds of patients demonstrate significant initial improvement after shunting (Malm et al., 2000; Hebb and Cusimano, 2001), although only up to one-third show sustained benefit at three years (Malm et al., 2000; Klassen and Ahlskog, 2011). Unfortunately, out of the key triad of impairments in INPH, dementia is the feature least likely to respond to shunting (Savolainen et al., 2002; Poca et al., 2004; Klassen and Ahlskog, 2011), particularly when cognitive impairment is severe or of long duration. One reason for this lack of response may be additional AD pathology, which of course is very common with older age even in the 'normal' population. However, benefits to gait appear to be independent of the presence or absence of AD pathology, and so, provided that patients and carers appreciate the limitations of surgical treatment, shunting for gait improvement alone may still be perfectly appropriate. Improvement also appears to be independent of age (Marmarou et al., 2005).

Key Points: INPH

- INPH is an uncommon, but potentially reversible, cause of dementia in old age.
- INPH should be excluded in patients with the classical triad of gait impairment, dementia, and urinary incontinence.
- All patients with INPH should have enlarged ventricles, but not all elderly patients with enlarged ventricles have INPH.
- After CT or MRI brain imaging, CSF removal and/or dynamic CSF testing are usually required before deciding on suitability for shunt insertion.
- Gait impairment is the feature most likely to improve after shunting.
- Dementia is less likely to be reversible where cognitive impairment is severe or of long duration, perhaps because of additional AD pathology; however, provided the risks are understood, shunting may still be considered for the benefits to gait alone.

Huntington's disease (HD)

Overview

HD is an inherited, autosomal dominant, neurodegenerative disorder resulting from an unstable expansion of a CAG trinucleotide repeat in the gene coding for the protein *huntingtin* on chromosome 4. The normal repeat number is between 6 and 35, and expansions of 40–44 repeats or greater lead to HD with 100% penetrance. The clinical features of HD usually emerge in early adulthood, but both juvenile and late-onset presentations are well recognized. HD is commonly associated with

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prominent psychiatric symptoms, and when it presents in old age the clinical syndrome may be atypical. The family history may also be obscured by factors such as death from other causes in an affected parent or sibling before clinical features of HD are manifest; missing or 'hidden' relatives with unrecognized HD, particularly relatives who committed suicide; and nonpaternity. Up to 10% of cases of HD may represent new mutations. For old age psychiatrists, an appreciation of the wide range of clinical features in HD is therefore important to avoid a missed or delayed diagnosis. The only assessment that definitively excludes HD is genetic testing.

Epidemiology

HD is one of the commonest inherited neurodegenerative illnesses, with a prevalence in most western European countries of 4-8/100,000 (Harper, 1986). Lower prevalences are seen in certain other countries (e.g. Finland) and ethnic groups (e.g. Afro-Caribbean populations), but essentially HD is found worldwide. The peak age of onset is between 35 and 44 years, but HD can present at any age. Both sexes are affected equally.

Clinical features

HD classically presents with the combination of a movement disorder and a frontal dementia. Typically, the initial movement disorder is hyperkinetic, with chorea or dystonia, later progressing to an akinetic-rigid state. However, some patients with late-onset HD may present with an akinetic-rigid syndrome from the outset, causing diagnostic confusion (Reuter et al., 2000). Other physical clues to the diagnosis include oculomotor abnormalities (e.g. slowed voluntary saccades and impersistence of gaze).

HD is also associated with a wide range of psychiatric and cognitive symptoms. The commonest psychiatric disturbance is depression, affecting 40-50% of patients with HD during the course of their illness. The suicide rate in HD is reported to be four to six times higher than in the general population, and in one early cohort of HD patients, suicide accounted for over 2% of deaths (Schoenfeld et al., 1984). Anxiety and obsessive-compulsive symptoms are also frequently reported. Psychosis is less common, but up to 10% of patients show psychotic symptoms at some stage in their illness, usually poorly systematized paranoia with behavioural changes such as aggression and irritability. An early age of onset may be associated with an increased risk of psychosis, and psychiatric disturbance can occasionally be the presenting feature of HD in younger patients (Lovestone et al., 1996). Frank auditory hallucinations of the type seen in schizophrenia are rare.

Cognitively, patients with HD show prominent deficits on tests of attention, semantic verbal fluency, processing speed, and executive function. Performance on tests of memory can be poor, but the profile of problems (with recall affected more than recognition) suggests difficulties

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with retrieval rather than encoding. Cognitive impairment can also be detected prior to diagnosis in gene-positive individuals at risk for the development of HD (Lawrence et al., 1998a,b).

Investigations

MRI in patients with HD may show generalized cortical atrophy or specific caudate atrophy (see Fig. 34.2). However, the only definitive investigation is genetic testing for the CAG expansion. This is a routine procedure, but because of the significant implications of a positive test for patients and their families, referral to clinical genetics services for counselling prior to testing is generally recommended.

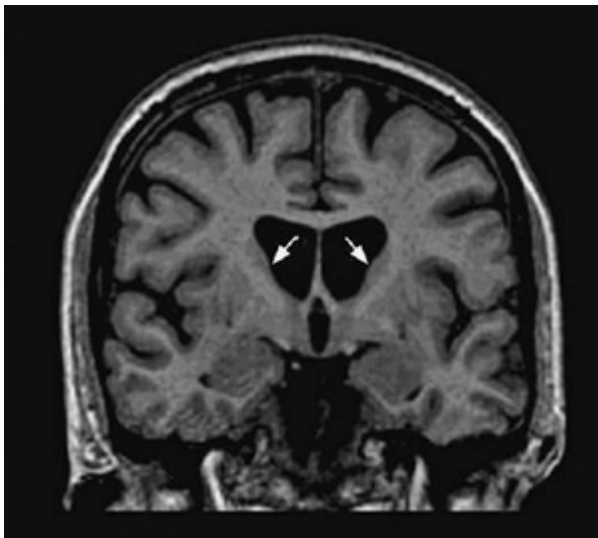


Fig. 34.2

Coronal FLAIR MRI in HD, showing bilateral caudate atrophy (arrows).

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Treatment and outcome

There is currently no cure for HD. Neuropsychiatric symptoms may all be treated with conventional medications, but many HD patients have an increased sensitivity to side effects. Longitudinal studies show a steady decline in cognitive function, with progressive functional disability and eventual death after an interval ranging from 10–30 years. Recently, there has been excitement about the prospect of genetic treatment in HD using anti-sense oligonucleotides (ASOs) injected by lumbar puncture to reduce the expression of the mutant huntingtin protein (mHTT) and modify the disease course. Initial studies show this approach is well tolerated, with a significant, dose-dependent reduction of mHTT in CSF of a magnitude

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that exceeds effective levels in animal models. However, it is too early to say whether this treatment will be of clinical benefit in humans.

Key Points: Huntington's Disease

- HD is an inherited, autosomal dominant, neurodegenerative condition that most usually presents with the combination of a frontal dementia and hyperkinetic movement disorder.
- Late-onset HD is well described and may present atypically, e.g. as an akinetic-rigid syndrome. Sometimes the family history is obscured or lacking.
- HD can only be completely excluded by genetic testing. Because of the implications of a positive test, it is usually wise to involve clinical genetics services prior to making a diagnosis.
- There is currently no cure for HD, although survival may be prolonged in some patients. Gene therapy trials hoping to modify the disease course are in progress.

Multiple sclerosis (MS)

Overview

MS is a chronic, relapsing, and remitting or progressive disease of the central nervous system (CNS) that involves both inflammatory/demyelinating and neurodegenerative processes. Symptoms are typically motor or sensory and intermittent and unpredictable to start with, later becoming progressive and disabling, but the disease course in MS is extremely variable. Most commonly, the initial pattern is of attacks affecting different sites in the CNS at different times, but with good recovery between attacks (relapsing-remitting MS). However, after a period of years, recovery after attacks tends to be less complete, leading to a gradual accumulation of fixed disability, followed later by steady deterioration irrespective of the frequency or severity of acute attacks (secondarily progressive MS). Occasionally, patients follow a steadily progressive course from disease onset (primary progressive MS). It is tempting to assume that reducing the frequency or severity of acute attacks would retard the progression of disability in MS, but unfortunately this is not necessarily the case. Increasingly, evidence suggests that neurodegeneration is taking place alongside inflammatory/demyelinating changes from an early stage (Chard et al., 2002). A primary progressive course, particularly with motor symptoms, may be more common in late-onset disease.

Epidemiology

The prevalence of MS varies widely according to geography and ethnic group, with the highest rates in populations of northern European descent. In a longitudinal study over 15 years in Olmstead County,

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Minnesota, the prevalence of MS was 177 per 100,000 of the adult population (Mayr et al., 2003); in a similar longitudinal study in Cambridge, UK, the prevalence was 152 per 100,000 (Robertson et al., 1996). MS is the commonest neurological disorder of young adults in the UK, with disease onset typically between the ages of 15 and 50 years. Later onset MS (age more than 50 years) is well recognized, although there is no consensus as to whether this refers to age at first symptoms or at diagnosis, and onset (however defined) is still usually before the age of 65 years. In a retrospective Israeli study of 640 patients cared for at a specialist MS centre, 30 (4.6%) had their first symptoms after the age of 50 (mean 53.5 years, SD 3.1, range 50–62) (Polliack et al., 2001), while a similar single-centre German study identified 52 patients over a ten-year period aged over 50 years at diagnosis (mean 57 years, SD 7, range 50–82) (Kis et al., 2008).

However, while MS presenting *de novo* to old age psychiatry with predominantly cognitive symptoms and onset after the age of 65 years is uncommon, two other scenarios are possible. First, patients with established MS may develop dementia in later life, either due entirely to their MS, additional degenerative disease, or a combination of both. In any of these situations, accurate diagnosis and management is likely to be more challenging. Second, the possibility of demyelinating disease may be raised on imaging investigations of dementia, especially with the sensitivity of MRI for white matter abnormalities. Over the age of 50 years, white matter changes are much more likely to be due to vascular disease than demyelination, but once the possibility of MS has been raised, careful clinical evaluation may be needed to exclude it.

Clinical features

Acute inflammatory/demyelinating attacks in MS may affect any site within the CNS, giving rise to an enormous breadth of possible clinical manifestations. The commonest symptoms involve motor, sensory, cerebellar, and visual/oculomotor systems, but neuropsychiatric and cognitive disturbance are also well described. The commonest neuropsychiatric disturbance is mood disorder (euphoria, mania, or depression); psychosis is rare, but recognized. Cognitively, impairment is generally most marked on tests of attention, processing speed, and executive function, followed by impairment on tests of verbal memory (recall more so than recognition). Language functions are generally better preserved, and frank aphasia secondary to MS is rare. In keeping with the presumed frontal/subcortical basis of this profile of deficits, a good predictor of cognitive impairment in MS is the degree of frontal lobe atrophy (Benedict et al., 2002). Cognitive impairment may occasionally be the presenting or only manifestation of MS (Zarei et al., 2003).

Investigations

The key investigation in suspected MS is an MRI scan, typically showing multiple high signal white matter lesions (Trip and Miller, 2005).

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However, as mentioned, high signal white matter lesions are a common finding in old age and may be entirely non-specific or reflect vascular disease. Radiological features that might specifically suggest demyelination include an ovoid shape to the lesions; involvement of the corpus callosum, brainstem, and cerebellum; and enhancement after contrast when lesions are acute (see Fig. 34.3); diagnostic criteria specify the profile of expected MRI abnormalities in MS very closely (McDonald et al., 2001; Thompson et al., 2017). Other supportive investigation results include unilateral or bilateral delay on visual evoked potentials (VEPs) and positive oligoclonal bands in CSF (but not serum) at lumbar puncture. Assessment of suspected MS and access to these secondary investigations will usually require referral to local neurology services.

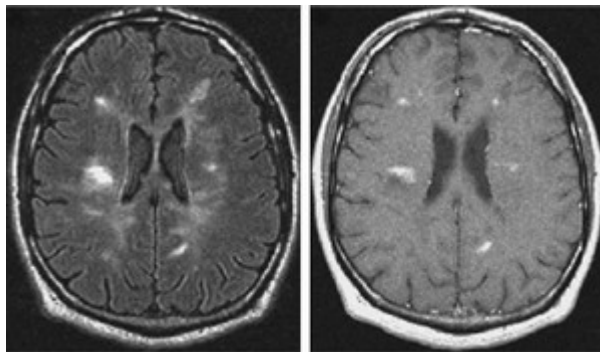


Fig. 34.3

MRI findings in MS. (Left) Axial FLAIR sequence showing multiple high signal periventricular white matter lesions, some transversely oriented; (Right) axial T1-weighted sequence showing that some of these lesions enhance after gadolinium, indicating active disease.

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Treatment and outcome

There is no curative treatment for MS. For acute relapses, a short course of corticosteroids may speed recovery but has no impact on the development of later disability. For patients with frequent disabling relapses, disease-modifying treatments are now available. The beta-interferons and glatiramer acetate reduce relapse rates by approximately a third; agents in development such as alemtuzumab may reduce relapse rates by up to two-thirds. However, once again, the impact of these treatments on the development of eventual disability remains to be shown, and all may be associated with significant side effects. Given the frontal/subcortical profile of deficits in dementia associated with MS, it

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might be expected that cognitive rehabilitation would be of benefit, but systematic studies in this area are lacking.

Key Points: Multiple Sclerosis

- MS may be associated with a variety of cognitive and psychiatric disturbances including dementia.
- MS is an uncommon cause of dementia in old age, but might be suspected in a patient with a clinically isolated syndrome or established MS in middle life who later goes on to develop a frontal-subcortical pattern of cognitive impairment.
- The key test in suspected MS is an MRI scan, but distinguishing between demyelination and vascular disease in old age can be difficult, and specialist assessment and/or secondary investigations (evoked potentials and CSF examination) are likely to be required for a definite diagnosis.

Antibody-mediated encephalitis

Overview

Antibody-mediated encephalitis is an umbrella term for a rapidly expanding group of inflammatory central nervous system disorders, commonly involving subacute cognitive impairment, behavioural disturbance, seizures, and movement disorder in association with autoantibodies against neuronal cell surface proteins, ion channels, or synaptic antigens. The spectrum is broad—some types of antibody-mediated encephalitis may present with a rapidly progressive dementia with neurological signs, while other types may present with purely psychiatric symptoms, at least in the early stages. Another key characteristic is that if recognized early, many of these disorders are potentially treatable.

The background to the discovery of the antibody-mediated encephalitides was the recognition over 50 years ago of the syndrome of limbic encephalitis (LE), with behavioural disturbance, memory impairment, and seizures related to inflammation of the limbic system. In the 1960s Brierley and colleagues (1960) reported three patients with non-specific prodromal symptoms, progressive cognitive impairment, coma, and death 3–14 months after onset; one patient additionally had focal seizures of temporal lobe origin. At post-mortem all showed evidence of a subacute encephalitis, mainly affecting the limbic system; one patient had malignant infiltration of mediastinal lymph nodes suggesting bronchial carcinoma. Corsellis and colleagues (1968) later reported three similar patients with prominent severe memory impairment and death up to 24 months after onset; two had focal and secondarily generalized seizures. All patients had encephalitis at post-mortem and underlying bronchial carcinoma. Investigators speculated at the time that the neurological

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syndrome might be an immunological reaction to the underlying cancer and subsequently a range of anti-neuronal antibodies were described in patients with LE and a tumour, principally anti-Hu in patients with small cell lung cancer (Dalmau et al., 1992); anti-Ma2 in patients with testicular tumours (Voltz et al., 1999); and anti-CV2/CRMP5 in patients with thymoma (Antoine et al., 1995). The discovery of these antibodies gave hope that patients with LE could be treated, but the response to immune therapy was generally disappointing and indeed it was uncertain as to whether the antibodies in these paraneoplastic conditions were truly pathogenic (Dalmau et al., 1992).

However, it was then recognized that some patients with LE showed antibodies of a quite different type, directed not against intracellular antigens but against cell surface ion channels such as the voltage gated potassium channel (VGKC). Furthermore, these antibodies were much less likely to be associated with cancer and the response to immune treatment could be very good (Thieben et al., 2004; Vincent et al., 2004). Subsequent work has identified that in fact anti-VGKC antibodies are directed against a range of VGKC-associated proteins rather than against the channel itself: key targets include LGI-1 (leucine-rich, glioma-inactivated protein 1), CASPR2 (contactin-associated protein 2) (Irani et al., 2010; Lai et al., 2010) and, less commonly, DPPX (dipeptidyl-peptidase-like protein) (Boronat et al., 2013). Finally, in the past decade the field of antibody-mediated encephalitis has exploded with the discovery of a whole range of novel antibodies directed against synaptic targets, e.g. the NMDA receptor (Dalmau et al., 2007; Dalmau et al., 2008), AMPA receptor (Lai et al., 2009) and the GABA-B (Lancaster et al., 2010; Hoftberger et al., 2013) and GABA-A receptors (Petit-Pedrol et al., 2014; Spatola et al., 2017). Some of these newer syndromes are less likely to present to psychiatrists (e.g., anti-GABA-B and anti-GABA-A encephalitis generally present with prominent seizures or new onset status epilepticus), but anti-NMDA receptor encephalitis is notable because it is quite distinct from typical LE and often has a psychiatric prodrome. For an up-to-date review, see Dalmau and Graus (2018)—key differences between the major antibodies discussed are summarized in Table 34.2 (not an exhaustive list).

Table 34.2 Antibodies associated with antibody-mediated encephalitis

Antibody	Commonly associated neurological syndrome(s)	Association with underlying cancer	Response to treatment (immune therapy or cancer removal)
Antibodies against ion channels			

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LGI-1	Typical LE Facio-brachial dystonic seizures	5-10% Thymoma	Excellent if immunotherapy instituted early
CASPR2	Typical LE	20-50% Thymoma	Variable
DPPX	Encephalitis with an exaggerated startle response	<10% Lymphoma	Requires prolonged therapy, may relapse
Other antibodies against cell-surface antigens			
Anti-NMDA receptor	Psychosis, cognitive and behavioural change, distinct from typical LE	Ovarian teratomas (younger women)	Improvement in up to 60%, but recovery typically prolonged
Anti-AMPA	LE	60-70% Thymoma, SCLC	Requires prolonged therapy, may relapse
Anti-mGluR5	Encephalitis	70% Hodgkin's lymphoma	Requires prolonged therapy, may relapse
Against intracellular antigens			
Anti-Hu	LE Cerebellar ataxia Subacute sensory neuropathy	SCLC (>90%)	Poor
Anti-Ma2	LE Brainstem encephalitis	Testicular germ-cell tumours (younger men) Non-SCLC, breast	Good in up to 30% (typically younger men with testicular germ- cell tumours)

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Anti-CV2/ CRMP5	LE Cerebellar ataxia Subacute sensory neuropathy	SCLC (>70%) Thymoma	Poor

LE, limbic encephalitis; VGKC, voltage gated potassium channel; LGI-1, leucine-rich, glioma-inactivated protein 1; CASPR2, contactin-associated protein 2; DPPX, dipeptidyl-peptidase-like protein; NMDA, N-methyl-D-aspartate; SCLC, small cell lung cancer.

Epidemiology

The incidence of antibody-mediated encephalitis is unknown. A prospective study of encephalitis in 24 hospitals in England between 2005 and 2008 gave an incidence for all forms of encephalitis (infectious and autoimmune) of between 2.73 and 8.66 cases/100,000/year depending on the modelling assumptions, with a best estimate of 5.23 cases/100,000/year (Granerod et al., 2010). Of 203 patients with encephalitis, 86 patients (42%) had infectious causes, including 38 (19%) with herpes simplex virus (HSV); while 42 patients (21%) had an immune mediated cause, including 16 (8%) with either anti-VGKC or anti-NMDA receptor antibodies (Granerod et al., 2010). These figures suggest that antibody-mediated encephalitis is less common than HSV encephalitis, but in a US study of 761 individuals with encephalitis referred to the California Encephalitis Project from 2007 to 2011, anti-NMDA receptor encephalitis was four times as common as HSV (Gable et al., 2012). After NMDA, anti-LGI1 encephalitis is probably the next most common individual antibody detected (van Sonderen et al., 2017). It is also notable that 75 patients (37%) in the UK prospective study had an unknown cause for their encephalitis. Given the range of new antibodies described in the last decade it is plausible that at least some of these patients had an undiagnosed antibody-mediated encephalitis.

Antibody-mediated encephalitis affects patients of all ages, although some forms such as anti-NMDA receptor encephalitis predominantly affect a younger age group. In a large, retrospective US study of encephalitis-related hospitalizations between 1998 and 2010 the estimated mortality rate for all causes of encephalitis was 5.8% (95% CI 5.6–6.0%), with a higher mortality of 17.1% (95% CI 14.6–20.0%) for patients with HIV infection, or a history of organ transplant (Vora et al., 2014). There is no single figure for mortality related specifically to antibody-mediated encephalitis, reflecting the heterogeneity of the condition and the rapidly expanding range of treatments available.

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Clinical features

Recognizing antibody-mediated encephalitis can be difficult. Sometimes it presents with a well-specified clinical syndrome such as classical limbic encephalitis, with subacute onset of behavioural disturbance, memory impairment, and seizures. When all features are present, LE is unlikely to be mistaken for a primary degenerative dementia. However, when features are present in isolation the diagnosis is more challenging. Anti-LGI1 limbic encephalitis may present with rather subtle memory disturbance and brief, lateralised spasms of the face and upper limb known as facio-brachial dystonic seizures. Anti-NMDA receptor encephalitis presents differently to classical LE, with more prominent psychiatric disturbance, followed by a variety of hyperkinetic movement disorders, and eventually coma.

Investigations

A common clinical problem is that even when an antibody-mediated encephalitis is suspected, it can be weeks before confirmatory autoantibody test results are available. Therefore, if suspicion is high enough, and key investigations such as MRI, CSF examination, and EEG are supportive, clinicians may choose to start treatment presumptively while waiting for the confirmatory tests.

Patients with anti-VGKC complex antibodies and classical LE tend to show abnormal high signal in the medial temporal lobes on MRI. However, imaging in patients with early disease or isolated clinical features, e.g. facio-brachial dystonic seizures, may be normal. In anti-NMDA receptor encephalitis imaging may be normal or show predominantly extratemporal abnormalities. The findings in paraneoplastic LE are variable. Typical MRI findings in patients with paraneoplastic and anti-VGKC complex antibody-associated LE are illustrated in Fig. **34.4**.

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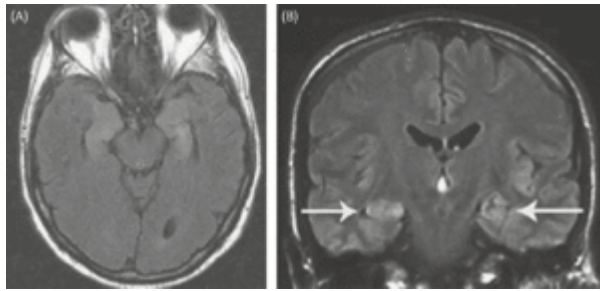


Fig. 34.4

MRI findings in LE. (A) Axial FLAIR sequence in paraneoplastic LE showing bilateral mesial temporal high signal change; (B) coronal FLAIR sequence in anti-voltage gated potassium channel LE showing high signal change in the hippocampi bilaterally (arrows).

A: Reproduced with permission from Dalmau, J. and Rosenfeld R. M. Paraneoplastic syndromes of the CNS. *The Lancet Neurology*, 7(4): 327–340. Copyright © 2008 Elsevier Ltd. All rights reserved. DOI: [https://doi.org/10.1016/S1474-4422\(08\)70060-7](https://doi.org/10.1016/S1474-4422(08)70060-7).

B: Reproduced with permission from Schott, J. M. Limbic encephalitis: a clinician's guide. *Practical Neurology*, 6(3): 143–153. Copyright © 2006 *Journal of Neurology Neurosurgery and Psychiatry*. DOI: <http://dx.doi.org/10.1136/jnnp.2006.091827>.

CSF examination may show a variety of abnormalities in all forms of antibody-mediated encephalitis, including a lymphocytosis or pleocytosis, raised protein, and (occasionally) unmatched CSF oligoclonal bands.

EEG may confirm focal cerebral dysfunction or epileptiform activity but is rarely specific for antibody-mediated encephalitis, except in the case of anti-NMDA receptor encephalitis where it may show a characteristic 'extreme delta brush' abnormality.

Combining clinical information with MRI, CSF, and EEG results, typical LE can be diagnosed and treatment started before confirmatory autoantibody test results are available. When typical features are missing, a confirmatory autoantibody test result is required. Probable anti-NMDA receptor encephalitis can be diagnosed from the combination of clinical information, CSF, and EEG results, but a definite diagnosis always requires a positive anti-NMDA antibody test (see Table 34.3).

Table 34.3 Clinical presentation, typical investigation findings, and suggested diagnostic criteria for limbic encephalitis and anti-NMDA receptor encephalitis

	Limbic encephalitis	Anti-NMDA receptor encephalitis

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Clinical presentation	Subacute onset¹ of symptoms suggesting involvement of the limbic system: • memory deficits • seizures • psychiatric symptoms	Subacute onset¹ of symptoms from the following six major groups of symptoms: • Abnormal (psychiatric) behaviour or cognitive dysfunction • Speech dysfunction (pressured speech, verbal reduction, mutism) • Seizures • Movement disorder, including dyskinesias or rigidity/abnormal postures • Decreased level of consciousness • Autonomic dysfunction or central hypoventilation
MRI	Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes ²	May be normal, or show extra-temporal abnormalities
CSF	CSF pleocytosis ³	CSF pleocytosis ³ or oligoclonal bands
EEG	Abnormal EEG with epileptic or slow-wave activity involving the temporal lobes	Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush)

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Diagnosis	Definite limbic encephalitis: Requires all four of 1. Typical clinical presentation as above 2. Bilateral temporal lobe abnormalities on MRI (or ¹⁸F-FDG PET) 3. Either CSF or EEG changes as above, or both 4. Reasonable exclusion of alternative causes If one of the first three criteria is not met, then a diagnosis of definite limbic encephalitis can only be made with the detection of antibodies against cell-surface, synaptic, or onconeural proteins	Probable anti-NMDA encephalitis: Requires all three of 1. Typical clinical presentation as above 2. Either CSF or EEG changes as above, or both 3. Reasonable exclusion of alternative causes Or: Systemic teratoma plus one or more symptom groups Definite anti-NMDA encephalitis can be diagnosed with one or more of the six major groups of symptoms above plus positive IgG anti-NMDA receptor antibodies,⁴ after reasonable exclusion of alternative causes

¹ Less than three months

² ¹⁸Fluorodeoxyglucose (¹⁸F-FDG) PET can be used to fulfil this criterion, by showing an increase in FDG uptake in normal-appearing medial temporal lobes

³ CSF white blood cell count of more than five cells per mm³

⁴ Antibody testing should include testing of CSF. If only serum is available, confirmatory tests should be included (eg, live neurons or tissue immunohistochemistry, in addition to cell-based assay). Source: data from Graus, F. et al. (2016) A clinical approach to diagnosis of autoimmune encephalitis *Lancet Neurol* 15(4):391-404. doi: 10.1016/S1474-4422(15)00401-9.

When should psychiatrists suspect antibody-mediated encephalitis?

Psychiatric disorder is common in antibody-mediated encephalitis (Schott, 2006). In a German study of 100 patients diagnosed with autoimmune encephalitis at a specialist centre, psychiatric symptoms were the

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commonest individual clinical feature; psychiatric symptoms were the first feature in 60% of patients; and one third of patients were initially hospitalized on a psychiatric ward (Herken and Pruss, 2017). However, discriminating early antibody-mediated encephalitis from a primary psychiatric disorder is challenging. The authors of the study above suggest several 'yellow flags' that may point to an autoimmune cause in new onset psychosis, including rapid progression despite therapy, headache, autonomic instability, focal neurological symptoms, hyperkinetic movement disorders, catatonia, reduced consciousness, hyponatraemia, and a past medical history of other autoimmune disease. In such cases antibody-mediated encephalitis should at least enter the differential. Facio-brachial dystonic seizures, generalized seizures, and suspected malignant neuroleptic syndrome are clear red flags and should prompt assessment with MRI, EEG, CSF examination, and antibody testing. With increased awareness of these conditions, and wider availability of antibody testing, diagnoses are being made more rapidly—in Herken and Pruss's study, for patients presenting between 2007 and 2012, the mean time from first symptoms to diagnosis was 483 days, compared to 74 days for patients presenting between 2013 and 2016. The as-yet unanswered question is whether antibody-mediated encephalitis is a significant cause of wholly psychiatric presentations with no atypical features such as first episode psychosis. In a prospective study of 228 patients with first episode psychosis and 105 healthy controls, 20 patients (9%) had positive antibodies compared to four controls (4%). Overall, this difference was not significant, but seven of the 20 patients had anti-NMDA receptor antibodies compared to none of the controls, raising the possibility that at least some patients with first episode psychosis have an autoimmune cause (Lennox et al., 2017).

Treatment and outcome

As indicated in Table 34.2, response to treatment in antibody-mediated LE very much depends on the associated antibody and whether the disorder is paraneoplastic. Patients with anti-LGI-1 antibodies and no underlying cancer respond the best to immunotherapy, which might include steroids, intravenous immunoglobulin, plasma exchange, and rituximab. However, if treatment is delayed, hippocampal atrophy may develop and clinical deficits become permanent. Seizures in LE tend to be rather resistant to conventional anti-epileptic drug treatment.

Key Points: Antibody-Mediated Encephalitis

- LE is a condition in which relatively selective inflammation or dysfunction of the limbic system leads to behavioural disturbance, subacute memory impairment, and seizures, classically associated with medial temporal lobe abnormalities on MRI.
- Anti-VGKC antibody-associated LE due to anti-LGI-1 antibodies tends to present with a full spectrum of clinical features,

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together with abnormalities on imaging, sometimes abnormalities on EEG and CSF examination, and often abnormalities of serum sodium; it may respond favourably to immune treatment if instituted early enough. Anti-CASPR-2 VGKC disease is more likely to be paraneoplastic and resistant to immunotherapy.

- Anti-NMDA receptor encephalitis presents rather differently to typical LE, with more psychiatric disturbance initially, sometimes relatively normal investigations, and a very variable course.
- Paraneoplastic LE is associated with a variety of antibodies to intracellular antigens, may be accompanied by other neurological syndromes such as sensory neuropathy and cerebellar ataxia, and tends to be resistant to treatment.

Prion diseases

Overview

The prion diseases are a heterogeneous group of disorders, neuropathologically characterised by the abnormal folding and accumulation of prion protein with accompanying spongiform degeneration. Prion diseases are rare but can present in a wide variety of ways, including with purely psychiatric symptoms.

Prion diseases develop by three mechanisms: spontaneously (sporadic); through exposure to affected tissue from the same or another species (acquired); and because of genetic mutations in the prion protein gene (familial). The majority of prion disease (~85%) is sporadic, involving the spontaneous conversion of normal cellular prion protein (PrP^C) into an abnormally folded and protease-resistant isoform (PrP^{Sc}). Abnormally folded PrP^{Sc} then acts as a template for the conversion of further PrP^C, and the process continues exponentially. As PrP^{Sc} accumulates there is accompanying neurodegeneration, and inexorable clinical progression; the commonest presentation of sporadic prion disease is a rapidly progressive dementia with ataxia and myoclonus (classical sporadic Creutzfeldt-Jakob disease, or sCJD). In acquired prion disease the conversion process is triggered by inadvertent exposure to abnormally folded PrP^{Sc}: either human-derived (causing iatrogenic CJD and the historical condition of *kuru* in the Fore people of Papua New Guinea), or bovine-derived (causing the completely distinct condition of variant CJD, or vCJD).

Phenotypic variability in sporadic and acquired prion diseases is influenced by multiple factors, particularly the pattern of polymorphisms in the prion protein gene (PRNP) and the physico-chemical properties of the accumulating PrP^{Sc}. For example, a common PRNP polymorphism at codon 129, while not being specifically disease-causing, strongly

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determines susceptibility to sCJD (Worrall et al., 1999): individuals who are homozygous for methionine (MM; 42% of the UK population) or valine (VV; 11%) are significantly more susceptible than individuals who are heterozygous (MV; 47%). At a molecular level, following limited protease digestion, at least two (Parchi et al., 1999), or four (Hill et al., 2003) different PrP^{Sc} isoforms can be identified, each linked to a distinct group of prion diseases. Combined with the pattern of PRNP codon 129 polymorphisms and the findings on histopathological examination, researchers have suggested various classificatory systems for the resulting prion *strains* (Gambetti et al., 2011; Wadsworth and Collinge, 2011; Parchi et al., 2011), but thus far none have been universally accepted (see Brandner, 2011; Cali et al., 2006 for a comparison). None of these systems can currently account for the finding of different prion strains in different brain areas in the same individual, nor accommodate familial prion diseases where the patho-biochemical properties of the accumulating prion protein are quite different to sporadic and acquired prion disease.

Iatrogenic CJD arises because although PrP^{Sc} is not a conventional infectious agent, exposure to human tissues or fluids containing PrP^{Sc} can initiate the process of PrP^C-to-PrP^{Sc} conversion in the recipient. The vast majority of cases of iatrogenic CJD to date have been reported either in patients exposed to PrP^{Sc}-contaminated human-derived growth hormone (prior to 1985), or patients receiving PrP^{Sc}-contaminated cadaveric dura mater grafts in neurosurgical procedures (prior to 1992). Transmission has also been reported with PrP^{Sc}-contaminated corneal grafts and neurosurgical instruments such as EEG depth electrodes.

vCJD arises because in certain circumstances transmission may even take place across species, leading to one of the most worrying UK public health disasters of recent decades. Scrapie, an endemic prion disease of sheep and goats in the UK, was never previously thought to be directly transmissible to humans. However, when nervous tissue from scrapie-affected sheep found its way into cattle feed, it sparked an epidemic of a novel prion disease of cattle in the UK in the 1980s and 1990s, termed bovine spongiform encephalopathy (BSE). Eventually, the total number of cattle definitely diagnosed with BSE in the UK was nearly 200,000, but the true number is likely to have been much higher; in total, four million asymptomatic cattle were slaughtered to halt the epidemic. During this time, over 600,000 cattle affected with BSE likely entered the human food chain (Anderson et al., 1996).

It was not long before patients with a novel type of CJD were recognized, often with purely psychiatric symptoms in the initial stages (Bateman et al., 1995; Britton et al., 1995). One of the key differences between classical sporadic CJD and vCJD is that tissues outside the nervous system can be affected. The BSE prion protein is hypothesized to enter the body through the gut, and PrP^{Sc} deposition can be seen in lymphoid tissue at a variety of sites, including the appendix (Hilton et al., 1998) and the tonsils. This also means that vCJD can potentially be transmitted between

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humans by exposure to affected non-nervous tissue, including via blood transfusion (Llewelyn et al., 2004).

Finally, approximately 10–15% of prion disease is familial, secondary to a variety of genetic abnormalities in the PRNP: including point mutations in the C-terminal domain, premature stop codon mutations, and the insertion of octapeptide repeats in the N-terminal domain. Different mutations can be associated with very different clinical phenotypes.

Epidemiology

Classical sCJD, the commonest form of human prion disease, has an approximate annual incidence of 1–2 per million population. There is little or no variation in incidence across geographical boundaries or ethnic groups. The mean age at onset is approximately 65 years (range 42–91), with a mean duration to death of four months (range 1–18) (Parchi et al., 1999).

Approximately 226 cases of iatrogenic CJD related to human-derived growth hormone and 228 cases related to dura mater grafts have been reported worldwide. The incidence has fallen steadily since the transmission risks were recognized in the 1980s/1990s, but iatrogenic CJD related to cadaver-derived growth hormone exposure can have an extremely long incubation period (range 5–42 years; mean 17 years); therefore, even though this treatment was stopped in 1985, cases still occur occasionally. Since 2013, four patients have died in the UK with definite or probable iatrogenic CJD (<http://www.cjd.ed.ac.uk/sites/default/files/figs.pdf>, accessed 12 March 2018). The incubation time may also be influenced by genetic factors. In a UK cohort of patients with growth hormone derived iatrogenic CJD, individuals with a PRNP codon 129 VV genotype tended to have a much shorter incubation period than those with MV or MM genotypes; this perhaps suggests that the contaminated tissue came from a patient with a VV subtype of sporadic CJD (Rudge et al., 2015). Survival in iatrogenic CJD related to cadaver-derived growth hormone exposure tends to be longer than sporadic CJD with death after 5–42 months (mean 14 months). Most of the contaminated dura mater grafts were implanted outside of the UK (two-thirds in Japan).

The mean age of onset in vCJD has so far been much earlier than for classical sCJD (median 27 years), but old age psychiatrists should not be complacent—of the first 100 patients with vCJD, the oldest was aged 74 years (Spencer et al., 2002). To date (March 2018), 178 cases of definite or probable vCJD have been reported in the UK, all of whom have died (with pathological confirmation of the diagnosis in 123 patients; <http://www.cjd.ed.ac.uk/sites/default/files/figs.pdf>, accessed 12 March 2018). From a peak of 28 deaths from definite or probable vCJD in 2000 the incidence rate has been steadily falling, with only two deaths in the past five years and no new diagnoses since 2014. On the face of it, a major epidemic of vCJD now looks unlikely, but we cannot be entirely complacent. First, a UK-wide anonymized study of appendix samples from

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operations in England between 2000 and 2012 found 16 samples positive for PrP^{Sc} out of 32,441 specimens; a prevalence of one in 2,000 (Gill et al., 2013). By extrapolation, there are tens of thousands of people in the UK who have been exposed to BSE prion protein but have not so far developed neurological disease. Second, all 177 patients diagnosed with definite or probable vCJD in the UK up until 2014 were homozygous for methionine (MM) at codon 129 of the PRNP gene. However, the 178th patient in the UK was heterozygous for methionine and valine (MV) (Mok et al., 2017). This raises the possibility that there may be a second wave of the vCJD epidemic still to come, affecting patients with an MV (or VV) genotype who have a longer incubation period. Finally, there is the potential risk of vCJD through blood transfusion. In the UK, 67 individuals are known to have received non-leukodepleted packed red cell transfusions from 18 patients who later developed definite or probable vCJD. To date, three of these recipients are believed to have contracted vCJD as a consequence: one with clinical disease diagnosed after death (Llewelyn et al., 2004), one with clinical disease diagnosed in life (Wroe et al., 2006), and a third patient with clinical disease notified in 2007. One further individual known to have been exposed to contaminated packed red cells died from non-neurological causes and was found to have abnormal PrP^{Sc} in his spleen and a lymph node at post-mortem (Peden et al., 2004). Finally, one individual with haemophilia who had received pooled factor VIII concentrate known to include donations from a patient with vCJD also showed abnormal PrP^{Sc} in his spleen at post-mortem (Peden et al., 2010). There have been no further clinical cases since 2007, and together with the measures put in place by UK blood transfusion services since the 1990s it is hoped that there will be no further transfusion-related transmissions. However, given the likelihood of a large pool of asymptomatic infected individuals and potentially long incubation times, further cases cannot be ruled out (Urwin et al., 2016).

Clinical features

Sporadic CJD classically presents with a rapidly progressive dementia with ataxia and myoclonus (>50% of cases), but alternative presentations are well recognized. Sometimes patients present with a pure cognitive syndrome (~15%), pure ataxia (~1%), visual disturbance (~5%), or psychiatric disorder (~5%) (Mead and Rudge, 2017). Iatrogenic CJD related to growth hormone exposure often presents with ataxia rather than a rapidly progressive dementia.

The typical clinical phenotype of vCJD is quite distinct from classical sCJD. In a retrospective case notes analysis of the first 100 patients diagnosed with vCJD in the UK, psychiatric symptoms were the first feature in 63 patients; neurological symptoms were the first feature in 15; and in the remaining 22 both psychiatric and neurological features were present from onset (Spencer et al., 2002). Common, early (<4 months from onset) psychiatric symptoms included dysphoria, withdrawal, anxiety, irritability, insomnia, and loss of interest. Agitation and aggression were common later symptoms. There was a wide range of

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rarer later psychiatric symptoms, including hallucinations, paranoid delusions, confabulation, and bizarre behaviours. Early neurological symptoms were uncommon and non-specific; for example, persistent, unpleasant pain without sensory disturbance affecting the limbs, face, or trunk. However, all patients subsequently developed neurological features; most commonly ataxia and dysarthria, with cognitive impairment later (median 4–7.5 months from onset).

The clinical features of inherited prion disease depend on the specific PRNP mutation. The E200K point mutation (the commonest mutation worldwide) results in a phenotype that is indistinguishable from classical sCJD. About a dozen different point mutations result in the phenotype of Gerstmann-Sträussler-Scheinker syndrome (GSS); a slowly progressive ataxia or parkinsonian syndrome with later dementia, often with prolonged survival. The D178N point mutation, combined with an M polymorphism at codon 129 of the affected gene, causes the rare syndrome of fatal familial insomnia (FFI), in which patients develop severe progressive insomnia followed by autonomic disturbance, with cognitive disturbance much later. Premature STOP codon mutations can present as progressive dementia with prolonged survival, mimicking Alzheimer's disease or frontotemporal dementia. Finally, octapeptide repeat insertion mutations may present with a classical sporadic CJD phenotype or GSS phenotype, depending on the repeat length.

Investigations

Box 34.1 shows the current European MRI-CJD Consortium criteria for the diagnosis of sporadic CJD (Zerr et al., 2009), which combines clinical criteria with the results of MRI, EEG, and CSF examination for the 14-3-3 protein.

Box 34.1 European MRI-CJD Consortium criteria for the diagnosis of sporadic CJD

Rapidly progressive dementia (obligatory) plus

I. Clinical signs

- 1 Myoclonus
- 2 Cerebellar or visual
- 3 Pyramidal or extrapyramidal
- 4 Akinetic mutism

II. Tests

- 1 PSWCs in EEG
- 2 14-3-3 detection in CSF

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3 High signal abnormalities in caudate nucleus and striatum or at least two cortical regions (temporal-parietal-occipital) either in DWI or FLAIR

Probable CJD

Rapidly progressive dementia and two out of I and at least one out of II

Possible CJD

Rapidly progressive dementia and two out of I and duration less than two years

PSWCs, positive sharp wave complexes; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery

Reproduced with permission from Zerr, I., and Kallenberg, K. Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. *Brain*, 132(10): 2659–68. Copyright© The Author(s) 2009. Published by Oxford University Press on behalf of Brain. DOI: <https://doi.org/10.1093/brain/awp191>.

Typically, in classical sCJD, DWI sequences show high signal change in the caudate and putamen, or multiple areas of the cortical ribbon (see Fig. **34.5**); the EEG is abnormal, classically with periodic sharp wave complexes (PSWCs); and at lumbar puncture, basic CSF constituents are normal, with negative oligoclonal bands, but raised CSF 14-3-3 protein levels. However, none of these tests are 100% sensitive and specific for sCJD; in particular, the 14-3-3 protein is just a marker for severe neuronal injury.

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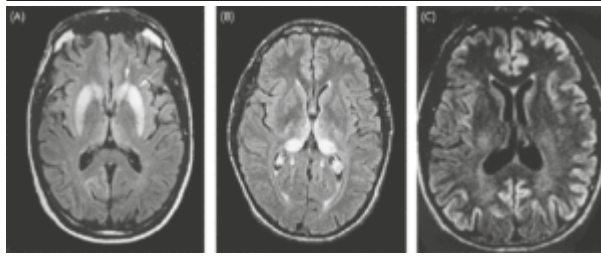


Fig. 34.5

MRI findings in sporadic and variant CJD. (A) Coronal FLAIR sequence in sporadic CJD, showing bilateral hyperintensity of caudate and putamen (arrows), but no signal change within the thalami; (B) coronal FLAIR sequence in variant CJD, showing the opposite pattern with bilateral hyperintensity of the thalami (arrows), but no signal change within caudate and putamen; (C) coronal FLAIR sequence in sporadic CJD, showing no deep nuclear changes but patchy bilateral hyperintensity of the cortical ribbon.

A/B: Reproduced with permission from Knight R. S. G., and Will, R. G. Prion diseases. *Journal of Neurology, Neurosurgery & Psychiatry*, 75(suppl 1): i36-i42. Copyright © 2004 *Journal of Neurology Neurosurgery and Psychiatry*. DOI: <http://dx.doi.org/10.1136/jnnp.2004.036137>

C: Reproduced with permission from Worrall, B. B., Herman, S. T., Capellari, S. et al. Type 1 protease resistant prion protein and valine homozygosity at codon 129 of PRNP identify a subtype of sporadic Creutzfeldt-Jakob disease. *Journal of Neurology, Neurosurgery & Psychiatry*, 67(5): 671-4. Copyright (c) 1999 Copyright © 1999, *British Medical Journal*. DOI: <http://dx.doi.org/10.1136/jnnp.67.5.671>

However, in the last few years a more specific test for the presence of misfolded prion protein has been developed: the real-time quaking-induced conversion test, or RT-QuIC. This test detects PrP^{Sc} by its ability to initiate the conversion of normal cellular PrP^C to misfolded PrP^{Sc} in vitro. Early studies showed that this method was similar in sensitivity but had superior specificity compared to 14-3-3 analysis (McGuire et al., 2012); second-generation RT-QuIC testing is up to 96% sensitive and 100% sensitive from CSF samples, can even be applied to nasal brushings (Zanusso et al., 2016), and is likely to replace 14-3-3 CSF analysis in future consensus criteria. The gold standard in sCJD is neuropathological examination with direct demonstration of abnormal PrP^{Sc} in brain tissue.

Investigation results in patients with vCJD are different to patients with sCJD. The EEG doesn't usually show the typical changes of sCJD, CSF 14-3-3 (and RT-QuIC) testing may be negative, and the pattern of MRI changes is different with high signal in the pulvinar nucleus of the thalamus (Mihara et al., 2005; see Fig. 34.5). As in sCJD, the gold

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standard is neuropathological confirmation of abnormal PrP^{Sc} in brain tissue, but as vCJD also affects lymphoid tissue outside of the CNS tonsillar biopsy in life may also be helpful in supporting a diagnosis (see Box 34.2).

Box 34.2 World Health Organization criteria for the diagnosis of variant Creutzfeldt-Jakob disease

I	A	Progressive neuropsychiatric disorder
	B	Duration of illness >6 months
	C	Routine investigations do not suggest an alternative diagnosis
	D	No history of potential iatrogenic exposure
	E	No evidence of a familial form of TSE
II	A	Early psychiatric features ^a
	B	Persistent painful sensory symptoms ^b
	C	Ataxia
	D	Myoclonus or chorea or dystonia
	E	Dementia
III	A	EEG does not show the typical appearance of sCJD in the early stages of illness ^c
	B	Bilateral pulvinar high signal on MRI scan
IV	A	Positive tonsil biopsy ^d

Definite: IA and neuropathological confirmation of vCJD^e

Probable: I and 4/5 of II and IIIA and IIIB; or I and IVA.

Possible: I and 4/5 of II and IIIA.

^a Depression, anxiety, apathy, withdrawal, delusions.

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^b This includes frank pain and/or dysesthesia.

^c The typical appearance of the EEG in sCJD consists of generalized triphasic periodic complexes at approximately one per second. These may occasionally be seen in the late stages of vCJD.

^d Tonsil biopsy is not recommended routinely, nor in cases with EEG appearances typical of sCJD, but may be useful in suspect cases in which the clinical features are compatible with vCJD and MRI does not show bilateral pulvinar high signal.

^e Spongiform change and extensive prion protein deposition with florid plaques throughout the cerebrum and cerebellum.

vCJD—variant Creutzfeldt-Jakob disease; TSE—transmissible spongiform encephalopathy; EEG—electroencephalography; MRI—magnetic resonance imaging.

(World Health Organization, 1998)

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A blood test for vCJD would be invaluable—either as a non-invasive test for patients with suspected clinical disease or to screen for preclinical infection—but the low level of PrP^{Sc} in blood makes this technically challenging. Candidate assays developed so far are highly specific for vCJD in clinically affected individuals but are not sensitive enough to use as a screening test (Edgeworth et al., 2011; Jackson et al., 2014). The key test in familial prion disease is obviously sequencing of the PRNP gene. In the UK, advice on the investigation and management of patients with suspected prion disease can be obtained through regional neurology services or the National Prion Clinic.

Treatment and outcome

There is no curative treatment for prion disease and all forms are ultimately fatal. Life-expectancy in classical sCJD is usually measured in weeks to months, but survival in vCJD or familial prion disease may sometimes be prolonged. Symptoms such as myoclonus and sleep disturbance may be palliated with appropriate medication.

Key Points: Prion Disease

- Prion disease is an uncommon cause of dementia in old age.
- The form of prion disease most likely to present to old age psychiatrists is classical sCJD, with the combination of a rapidly progressive dementia, ataxia, and myoclonus; vCJD typically

presents with neuropsychiatric symptoms, and neurological signs later.

- Positive investigations in prion disease include abnormal signal change on MRI, PSWCs on EEG, and 14-3-3 protein in the CSF, but the yield of these tests depends on the age of onset, disease duration, and underlying molecular subtype (Collins et al., 2006). Next-generation CSF testing with the RT-QuIC assay will likely replace 14-3-3 analysis in future diagnostic criteria. Tonsillar biopsy is an option in suspected vCJD.
- Definitive diagnosis can only be achieved by neuropathological examination, or in familial cases, sequencing of the PRNP gene.
- The prognosis in late-onset classical sCJD is uniformly poor, with deterioration and death in months. There is currently no effective treatment.

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Pharmacological treatment of dementia

Chapter: Pharmacological treatment of dementia

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Introduction

This chapter considers specific pharmacological treatment of dementia and summarizes the available clinical evidence with an emphasis on practical considerations and realistic expectations of the currently available antidementia drugs. Other topics, such as the treatment of motor symptoms for people with Parkinson's disease dementia (PDD) or dementia with Lewy bodies (DLB), vascular dementia (VaD), or fronto-temporal dementia (FTD) are discussed more briefly given these are covered elsewhere (e.g. Chapters 31–33). The chapter also considers drug treatments for mild cognitive impairment (MCI), but not the general management of this condition nor more specifically MCI due to Alzheimer's disease (Albert et al., 2011), also known as prodromal Alzheimer's disease (Dubois et al., 2010) as these are covered elsewhere (see Chapter 29 and Chapter 30).

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Finding treatments for dementia has concentrated on Alzheimer's disease (AD), partly because it is the commonest cause of dementia and partly because scientific progress has provided more potential therapeutic targets for AD than other dementias. Many neurochemical studies have been carried out in AD looking at specific neurotransmitters and a number of approaches have been investigated; the changes in acetylcholine are particularly consistent and significant. In this context the cholinergic hypothesis (Francis et al., 1999) suggests that AD results from a selective loss in cholinergic neurones, especially within the basal forebrain and neocortex resulting in decreased acetylcholine (ACh) levels: strategies to enhance these levels provide a logical treatment target. Acetylcholinesterase (AChE) is the principal enzyme that breaks down ACh and the first drugs licensed specifically for use in AD were AChE inhibitors (AChEIs).

By analogy with Parkinson's disease (PD), where there is dopaminergic deficiency, it would be expected that replacement therapies could potentially enhance residual synaptic activity. While replacement therapy may be important, it would only be expected to provide symptomatic benefit and not affect the underlying disease process.

In PD patients with cognitive impairment, there is cell loss in the cholinergic basal nucleus of Meynert and a cortical deficit in AChE that correlates with the severity of dementia and is independent of any coexisting AD (Bohnen and Albin, 2011). Patients with DLB also show a severe loss of choline acetyltransferase in the cerebral cortex that is even greater than that found in AD and this correlates with the severity of the dementia (Lippa et al., 1999). Such deficits therefore suggest a possible therapeutic role for cholinergic therapies in both PDD and DLB.

Glutamate, the principal fast excitatory neurotransmitter in the CNS, is the neurotransmitter of the neocortical pyramidal cells, neurones that are selectively lost in AD (Francis et al., 1993). Glutamate may be important in the pathogenesis of dementia for several reasons, including its activity at the N-methyl-D-aspartate (NMDA) receptor (Danysz et al., 2000), which is capable of long-term potentiation, a key element of memory formation, and therefore another potential therapeutic target. Memantine is the only other licensed treatment to date involving a neurotransmitter approach and it acts as an uncompetitive antagonist at the NMDA receptor (Danysz et al., 2000).

Treatment of Alzheimer's disease

Cholinesterase inhibition

Changes in the cholinergic system in AD have been known for many years. Several therapeutic approaches to stimulate the cholinergic system have been tried but AChEIs are the only compounds to have shown consistent efficacy in both clinical trials and clinical practice. In 1993, tacrine became the first agent specifically approved for treating the

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cognitive symptoms of AD in countries such as the US and Sweden but not in the UK. While the efficacy of tacrine in mild to moderate AD was clear (Arrieta and Artalejo, 1998), there were problems with its dosing frequency and tolerability, especially with a reversible hepatotoxicity, and it has been supplanted by later AChEIs.

Three other AChEIs are licensed for use in AD in most countries: donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl), and all three drugs have now reached the end of their patent lives so that generic forms are also available. AChEIs block the hydrolysis of acetylcholine at the synapse, increasing its availability to muscarinic and nicotinic receptors. All three are active against AChE, the principal form of the enzyme. Rivastigmine is also active against butyrylcholinesterase while galantamine appears to be an allosteric modulator of nicotinic receptors in animal models. It has been suggested that these subsidiary actions may lead to different clinical effects, although this has never been convincingly demonstrated. They are licensed in the UK for use in mild to moderate dementia in AD. Donepezil is also licensed for severe AD in some countries, including the US, where high-dose rivastigmine skin patches (13.3mg/24h) are also approved for severe AD, but neither is licensed for severe disease in Europe. Rivastigmine is also approved in the UK for mild to moderate dementia in PD.

Donepezil

Licensed in the UK in 1997, donepezil is the most widely used AChEI and has been studied the most intensively. It is beneficial for people with mild, moderate, and severe AD (Birks and Harvey, 2018), and is associated with improvements in cognitive function and activities of daily living (ADLs). The effects on cognition remained measurable and statistically significant at 52 weeks in one placebo-controlled study (Winblad et al., 2001). A Cochrane review (Birks and Harvey, 2018) suggested that 10mg was marginally better than 5mg and that the lower dose may be preferable because of improved tolerability, but clinically most patients are titrated to 10mg if possible. It is the simplest to use with an effective initial dose, one dose titration, and no interaction with food. Dosing up to 20 mg has been used by clinicians and a 23mg dose has been developed and approved by the FDA in the US. The 23mg/d dose improved cognition compared with 10mg/d in a 24-week study but there was no significant between-treatment difference for global functioning and there were more adverse effects and withdrawals at the higher dose (Farlow et al., 2010). Approval of this higher dose formulation has been controversial: Cummings and colleagues (2013) advocated the availability of the 23mg formulation, but it should be noted that Eisai sponsored the meeting where that paper was developed. In contrast, Schwartz and Wolosin (2012) regarded it as unjustified on both efficacy and safety grounds and argued that the sole purpose was to provide additional patent protection for a dose that cannot be achieved with 5 or 10mg tablets. Birks and

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Harvey (2018) also concluded that 23mg daily offered no benefits and was associated with more side effects.

Formerly, it was recommended to discontinue AChEI treatment when dementia became severe. However, this has changed since Howard and colleagues (2012) studied donepezil and memantine in moderate to severe AD (DOMINO), which found that continued treatment with donepezil was associated with cognitive and functional benefits over the course of 12 months in patients where the clinician was considering a change in drug treatment (i.e., stopping donepezil or introducing memantine). In addition, withdrawal of donepezil increased the risk of nursing home placement during the 12 months of treatment, but it should be noted that it made no difference during the following three years of follow-up (Howard et al., 2015). The authors suggest that decisions to stop or continue donepezil should be informed by potential risks of withdrawal even if perceived benefits of continued treatment are not clear. It is now recommended that AChEIs should not be stopped on the basis of disease severity alone (NICE, 2018).

Rivastigmine

Rivastigmine was licensed in the UK in 1998 for the treatment of mild to moderately severe AD. Capsules are given twice daily with food commencing at a non-effective dose of 1.5mg bd and increasing gradually and according to tolerability at a minimum of 2-weekly intervals to a maximum of 6mg bd. The efficacy of oral rivastigmine has been clearly demonstrated but adverse effects such as nausea and vomiting, especially at higher doses, are more frequent, for example, by comparison with donepezil. Since rivastigmine is a small molecule and both lipophilic and hydrophilic, it is well suited for transdermal delivery and once daily patches (4.6mg, 9.5mg, and 13.3mg/24 h) have now been widely licensed, including in the UK.

A Cochrane review by Birks and colleagues (2015) concluded that, based on seven clinical trials, rivastigmine 6–12mg/d orally and 9.5mg/24h transdermally appears to be beneficial for people with mild to moderate AD after six months treatment (it should be noted that they did not review the 13.3mg/24h patch). In comparison with placebo, better outcomes were seen for rate of decline of cognitive function and ADLs, although the effects were small and of uncertain clinical importance. There was also a benefit in the clinician's global assessment, but no difference for behavioural changes (three trials) or impact on carers (one trial). At doses up to 9.5 mg daily the transdermal patch had fewer side effects than capsules, but had comparable efficacy. The review assessed the quality of the data as moderate for all the outcomes reviewed because of a risk of bias due to dropouts for rivastigmine (Birks et al., 2015). One study comparing the 13.3mg patch with the 9.5mg version showed significantly reduced deterioration in instrumental ADLs with similar skin

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tolerability but a higher incidence of cholinergic gastrointestinal adverse effects (Cummings et al., 2012).

The skin patch, certainly at lower doses, presents fewer tolerability problems, e.g. gastrointestinal adverse effects, than oral rivastigmine and offers an alternative dosing route that may be preferred by, and for, some patients, but is more expensive. Application site reactions may occur, although these are usually mild or moderate in intensity and not generally an indication of sensitization. However, use of rivastigmine skin patches may lead to allergic contact dermatitis, which in some cases may indicate sensitivity to rivastigmine exposure such that rivastigmine in any form cannot be taken (Electronic Medicines Compendium UK, 2018).

Galantamine

Galantamine was licensed in the UK in 2000 for the treatment of mild to moderately severe AD. The drug is usually prescribed in a modified-release form as capsules of 8mg, 16mg, and 24mg, to be administered once daily.

Galantamine improves global and cognitive symptoms at doses of 16mg/day or greater for at least six months in people with mild to moderate AD (Loy and Schneider, 2006). Although there are no long-term placebo-controlled trials, a more recent analysis suggested that patients demonstrating improvement, stability, or limited cognitive decline after two to five months at their maintenance dose were more likely to experience longer-term continued benefit with galantamine (Kavanagh et al., 2011). Its safety profile in AD is similar to other AChEIs with respect to cholinergically mediated gastrointestinal symptoms (Loy and Schneider, 2006). The prolonged-release once-daily formulation at 16–24mg/day was found to have similar efficacy and side-effect profiles as the equivalent twice-daily regime (Loy and Schneider, 2006). Galantamine can rarely cause serious skin reactions (including Stevens-Johnson syndrome and acute generalized exanthematous pustulosis) and the manufacturer advises discontinuation at the first appearance of skin rash (BNF, 2019).

Adverse effects of cholinesterase inhibitors

The principal difference between the three AChEIs is in the frequency and type of adverse events (O'Brien et al., 2017). The main side effects are gastrointestinal, particularly anorexia, nausea, vomiting, and diarrhoea, as would be expected given the cholinergic enhancement provided by the compounds. Weight loss is also seen with galantamine and rivastigmine. These side-effects are most likely soon after treatment is commenced or when the dose is increased, hence the reason the drugs are all titrated up over a number of weeks.

Compliance with therapy is always a potential issue, especially in older patients who are also likely to be taking several other medications. There are particular issues if rivastigmine capsules have been omitted for a few

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days since re-titration up from 1.5mg twice daily must occur. This follows a reported case of severe vomiting and a ruptured oesophagus in someone restarted straightaway at a high dose (Babic et al., 2000). This re-titration also applies if rivastigmine skin patches have been omitted for a few days. The rivastigmine skin patch may be helpful for people who cannot tolerate an oral dose of an AChEI as gastrointestinal side-effects are reduced but skin sensitivity may occasionally be a problem instead (discussed earlier) and also overdose resulting from a failure to remove each day's patch, which has been associated with serious adverse reactions, hospitalization, and even death (Electronic Medicines Compendium, 2018). Donepezil may cause abnormal dreams and this can be reduced by giving the drug in the morning rather than at night—though conversely, night-time administration may mitigate any dizziness or hypotension associated with AChEIs. In addition, donepezil may cause muscle cramps and galantamine muscle spasms.

Adverse interactions with other drugs have not generally been an issue, although it is important that everyone is aware of the therapy they are receiving and to mention this when any other medical issue arises because of their role as cholinergic stimulants. Care should be exercised in patients with reversible airways disease or peptic ulcer disease and in those with cardiac conduction defects or significant bradycardia as the compounds increase vagal tone. Given the potential for AChEIs to slow the heart rate, some clinics routinely obtain ECGs before prescribing these drugs. However, the available evidence suggests that this is not necessary (Rowland et al., 2007; NHS Yorkshire and Humber Clinical Networks, 2016). What is recommended is checking the pulse, and then avoiding AChEIs if the heart rate is less than 50 beats/minute, and investigating patients who are symptomatic, but otherwise prescribing for patients who do not have cardiovascular symptoms.

Switching from one AChEI to another

The rationale for switching from one AChEI to another is that they are from different chemical classes and with slightly different pharmacological properties. The main reason for switching is because of poor tolerability, usually gastrointestinal, and the hope that an alternative compound will avoid this. There is no easy way of identifying subjects in advance who are likely to respond to an AChEI but differences, for example, in individual metabolism of a drug may lead to higher or lower drug levels, which could improve efficacy but possibly at the risk of side effects. One study has suggested that functional polymorphisms in the *CYP2D6* gene can influence the clinical efficacy of donepezil (Seripa et al., 2011). A significantly higher frequency of gene variants conferring decreased or absent enzyme activity were observed in responders in comparison with non-responders (73.7% versus 36.8%; $p = 0.005$); it might be predicted that 'non-responders' would be able to tolerate a higher dose of donepezil because of their enhanced metabolism of the

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compound and that more patients would then show a positive response to the compound.

Few studies of switching have been carried out, and all switching has been from donepezil; no recent or double-blind studies are available. However, it does appear that a proportion (up to 50%) of patients may benefit from a switch (O'Brien et al., 2017) and a change of formulation (particularly from a standard oral form to either a transdermal patch, or oral solutions that are available for all three drugs, or the orodispersible form of donepezil) does offer additional opportunities to find a treatment that is tolerated satisfactorily, and particularly in subjects where swallowing tablets or capsules is a problem. NICE (2018) has recommended that memantine should be considered as an alternative to an AChEI in moderate AD if there are contraindications or tolerability issues.

N-methyl-D-aspartate receptor antagonism

Memantine

Memantine is a non-competitive moderate affinity antagonist at the NMDA receptor. It is believed to restore glutamatergic neuronal transmission to physiological levels while preventing the effects of tonic pathologically elevated synaptic glutamate levels that may lead to neuronal dysfunction and damage (Danysz et al., 2000). Memantine was licensed in the UK in 2002 for the treatment of moderately severe to severe AD but this licence was subsequently extended to cover moderate dementia in AD. Initially recommended for 10mg twice daily dosage, clinical trials later demonstrated that 20mg once daily dosing was identical (e.g. Jones et al., 2007); the dosage has now been modified to once daily dosing beginning with a non-effective dose of 5mg and increasing to 20mg over a four-week titration period. Either 10mg or 20mg is an effective dose and it is still possible to give 10mg twice a day if this is more convenient (e.g. if patients are also receiving rivastigmine or galantamine twice daily); a memantine oral solution is also available.

Memantine is currently recommended as an option in moderate AD for those for whom AChEIs are contraindicated or where tolerability is poor, or in severe AD (NICE, 2018). Indeed, it is the only drug licensed in the UK for severe AD. A recent consensus statement confirmed that there is type I evidence (from meta-analysis of randomized, controlled trials) that memantine is an effective treatment for moderate to severe AD (O'Brien et al., 2017). Memantine is well tolerated and slightly fewer patients with moderate to severe AD taking memantine develop agitation in comparison with placebo (McShane et al., 2006).

One of the striking features of clinical trials with memantine has been that adverse events are often similar to placebo (in contrast to AChEIs) and, in general, gastrointestinal side effects are uncommon (but include constipation in contrast to the diarrhoea which is a common side effect of

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AChEIs). Memantine is thus generally extremely well tolerated (Jones, 2010) and therefore may be especially suitable for older and/or frailer patients, although hypertension has been reported as a common adverse event (in up to 10% of patients) so care should be shown in people with poorly controlled hypertension. Caution is recommended in patients with epilepsy or predisposing factors to epilepsy, and concomitant use of other NMDA antagonists (e.g. amantadine, ketamine, and dextromethorphan) should be avoided. The maximum daily dose should be 10mg in patients with severe renal impairment (with an estimated glomerular filtration rate (eGFR) of 5–29ml/min/1.73m²) and memantine should be avoided altogether if the eGFR is less than 5ml/min/1.73m².

Add-on or combination therapy of AChEIs with memantine

Simultaneous initiation of therapy with an AChEI and memantine has not been studied. This may partly be explained by their different licensed indications being mild to moderately severe AD for AChEIs and moderate to severe AD for memantine. Although it might be useful to know whether using lower doses of both types of drug would lead to similar or increased efficacy compared with full doses of either drug alone, in practice, prescribers are likely to start with a single drug in order to assess potential side effects. Adverse events, particularly gastrointestinal problems, might be reduced by combination therapy, especially if this enables treatment with lower doses, and this was seen in subjects receiving memantine and donepezil compared with placebo and donepezil in one memantine add-on study (Tariot et al., 2004). This may reflect either that memantine has some intrinsic cholinergic effects or that it offers protection to septal area cholinergic neurons (Colom et al., 2013), although these observations are from animal work so of uncertain clinical relevance.

There are no published studies investigating the addition of an AChEI to patients already established on memantine, which is probably because patients are usually commenced on an AChEI first, with memantine being considered as a later alternative or additional treatment; increasingly in countries like the US, adjunctive therapy with memantine is being commenced in patients who still have mild AD.

The evidence of the benefits of adding memantine to an AChEI is largely favourable, although the evidence is not strong, and whether any additional effects are clinically important remains questionable. A group from the European Federation of Neurological Societies reviewed four trials, comprising 1549 patients with moderate to severe AD, and found statistically significant improvements in global outcomes, cognition and behaviour (Schmidt et al., 2015). Despite grading the evidence as weak, the group recommended the use of combination therapy. The British Association for Psychopharmacology (O'Brien et al., 2017) also favoured combination treatment with a recommendation of grade B (range A to D). NICE (2018) recommended that, in patients with moderate AD, adding

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memantine should be *considered*, and in severe AD, combination treatment with memantine should be *offered*.

The DOMINO study in the UK found that starting memantine at the time donepezil was discontinued was better than not adding memantine, but adding memantine while continuing with donepezil did not seem significantly better than donepezil alone (Howard et al., 2012). This study was criticized (Tariot, 2012) partly because of the marked placebo decline in subjects randomized to receive neither memantine nor donepezil. Also, that there was no evidence for the lack of adjunctive memantine therapy based on the small sample sizes at the study end and the differential dropout rates between the groups. Subject recruitment was significantly lower than planned with a marked dropout rate even in the group that continued with donepezil, where only half of the patients continued the treatment for the entire one-year study period (Schneider, 2012). Unfortunately, such a trial is unlikely to be repeated, yet more information is still required about long-term benefits, safe discontinuation of AChEIs, and the role of combination therapy with memantine (Schneider, 2012).

In summary, in many countries, combination therapy with an AChEI initially, followed by the later addition of memantine, is now accepted as the optimal treatment for patients with AD, especially as the dementia progresses.

Practical considerations and realistic expectations of treatment in AD

How early should treatment be initiated?

Although the AChEIs are only licensed for people with a diagnosis of AD, some clinicians do commence treatment for people with MCI, where many but not all subjects will go on to develop a dementia, usually AD, in the coming years. The evidence to support this is poor, with several negative trials with different AChEIs and, indeed, in two placebo-controlled MCI trials of galantamine there was an unexplained excess death rate in the drug-treated group (Loy and Schneider, 2006).

Clinical relevance of benefits

It is by now well established that AChEIs and memantine produce statistically significant differences when compared to placebo in clinical trials. However, an important question is how clinically relevant such benefits are, and also to what extent might effects seen in trials also operate in routine clinical practice, given that trial participants are often healthier and better motivated than other members of the population from which they are drawn. Howard and colleagues (2011) estimated that the minimum clinically important difference (MCID) on the standardized Mini Mental State Examination was 1.4 points. In an extensive review of AChEIs and memantine, Tricco and colleagues (2018) found that only donepezil achieved a MCID for cognitive outcomes. Galantamine led to a

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clinically relevant global outcome, but there were no significant improvements in function from any individual drug or combination treatment with memantine. At an anecdotal level, clinical experience suggests that AChEIs sometimes lead to a noticeable improvement in attention and motivation, often for a period of several months, and this also seems like a worthwhile effect.

Less than expected decline

In a chronic progressive neurodegenerative disease like AD, improvements in symptoms are important. The evidence suggests that some 40–75% of patients experience a significant benefit from AChEIs, but it is difficult to predict in advance who will respond. There may be an initial, usually relatively short-term, improvement above baseline, but stabilization or less than expected decline are more realistic therapeutic targets. A patient treated early and persistently with medication would be expected to show less evidence of behavioural, functional, and cognitive deterioration over a period of time; there is substantial evidence that this is the case for the currently available drug treatments for AD (Geldmacher et al., 2006). For example, using a definition of marked clinical worsening for a patient showing cognitive decline (equivalent to the average natural decline in moderate to severe AD patients over six months) plus any decline in both ADLs and global function, 30% of patient on placebo showed clinical worsening at six months in comparison with only 14% on donepezil (Wilkinson et al., 2009). For memantine, 21% of patients showed a significantly greater degree of worsening on placebo in comparison with 11% on memantine (Wilkinson and Anderson, 2007). The DOMINO study also provided further support that patients who are declining while taking a drug for AD may still be benefiting by comparison with patients not on therapy (Howard et al., 2012).

However, it is difficult in clinical practice to decide whether or not treatment is beneficial for an individual patient. There is great variation between individuals and there are fluctuations in test performance that are of similar magnitude to the likely therapeutic effects. Thus, in practice, it is important to treat the patient and not be governed too much by scores on cognitive tests. If appropriate, therapy may be withdrawn for a short period or the dose reduced to see if there is a change in the patient's condition, but this is often very subjective and largely depends on the primary caregiver's opinion.

For an individual patient, slowing the rate of decline may have important consequences, e.g. reduced caregiver stress and delayed nursing home placement (Lopez et al., 2009). However, it is important that the patient, caregiver, and others—such as the primary care physician—have realistic expectations of the treatment. Since patients may improve very little, stabilize, or even decline, despite benefiting, people may become disillusioned if they have not been warned about this; this may affect compliance or lead to premature withdrawal of therapy.

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Withdrawal of treatment

Given the discussion above, there is no justification in withdrawing treatment with either an AChEI or memantine merely because of the progression of the dementia. The decision to withdraw treatment, or try to withdraw treatment, should be made on an individual basis when it is considered that the treatment may potentially be causing adverse effects or at a time when the dementia has advanced to a point where withdrawal of other therapy is also being considered. It is advisable to reduce the dose gradually where possible, since deterioration may occur and the drug may need to be reinstated.

Treatment of non-Alzheimer dementia

Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD)

Patients with DLB or PDD have a severe deficit in cortical ACh levels so that AChEIs might be expected to help. Rivastigmine is licensed in the UK, US, and elsewhere for mild to moderately severe dementia in people with idiopathic PD. Donepezil now has a marketing authorization for DLB in Japan and the Philippines based on a 12-week double-blind phase III study with open-label extension (Mori et al., 2015), but all other prescribing for DLB remains off-label.

Nonetheless, there are current recommendations for prescribing AChEIs and memantine for patients with DLB. O'Brien and colleagues (2017) gave a grade A recommendation for the use of donepezil or rivastigmine in DLB and PDD, and a grade B recommendation for memantine. Following from this, the current NICE (2018) guidance is: offer donepezil or rivastigmine to people with mild to moderate DLB; only consider galantamine in mild to moderate DLB if donepezil and rivastigmine are not tolerated; consider donepezil or rivastigmine in severe DLB; and consider memantine for people with DLB if AChEIs are not tolerated or are contraindicated.

For PDD, NICE (2017) advises: offer a cholinesterase inhibitor for people with mild or moderate PDD; consider a cholinesterase inhibitor for people with severe PDD; and consider memantine for people with PDD only if cholinesterase inhibitors are not tolerated or are contraindicated.

Visual hallucinations and visuoperceptual deficits are common to both PDD and DLB, together with fluctuating attention. The combination of cognitive, neuropsychiatric, motor, and autonomic features in DLB causes considerable functional decline. Treating neuropsychiatric features such as hallucinations may exacerbate parkinsonism, while antiparkinsonian medications may exacerbate psychosis. There is variability both between individuals and as the disease progresses, so that getting the right combination of therapies is challenging. Patients with DLB generally do not respond well to antiparkinsonian medication. One small study (Goldman et al., 2008) suggested that around a third of subjects did

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obtain a good motor response to L-dopa; however, a third of these also experienced a worsening of hallucinations or the development of psychosis. Side-effects must be monitored carefully and the dose increased slowly, avoiding high doses. Other antiparkinsonian medications should be used extremely cautiously because of the likelihood of inducing confusion and psychosis (Goldman et al., 2008).

There are still relatively few trials in DLB and PDD but there are several comprehensive reviews of the treatment of DLB and PDD and meta-analysis of trials (e.g. Stinton et al., 2015; Wang et al., 2015). AChEIs seem to benefit global and cognitive outcomes whereas memantine has only produced change in global ratings rather than cognition. The recent consensus statement (O'Brien et al., 2017) supported the use of donepezil and rivastigmine in DLB and PDD with the strongest recommendation (grade A), and for memantine with a grade B recommendation for producing global improvement in DLB and PDD but with the pattern of cognitive and neuropsychiatric responsiveness remaining uncertain. The current NICE guidance quoted earlier in this section reflects these findings.

Vascular dementia (VaD)

Managing vascular risk factors

No specific antidementia treatments are licensed for VaD, so it is important to focus on managing the underlying cardiovascular risk factors, including hypertension, diabetes, heart disease, and hypercholesterolaemia; these should be treated whenever possible, particularly in younger people. It can be hard to decide at what stage in life cardiovascular prevention is no longer worthwhile. Lipid-lowering therapy is probably inappropriate for a person with a life expectancy of fewer than two years or where there is an irreversibly poor quality of life; at this stage, end-of-life care becomes more important, but all such decisions should be made individually and not on the basis of age alone.

There is good evidence for the effectiveness of treating hypertension in older people but clinicians are often reluctant to do so. In extreme old age, lower blood pressure is associated with increased mortality, but there is at least one RCT (the SPRINT trial) of people aged over 75 in which treating hypertension was associated with better outcomes (Williamson et al., 2016). There may be concerns about compliance and also the risk of side effects, e.g. postural hypotension. Successful blood pressure control can enhance cognitive performance in patients with multi-infarct dementia (Meyer et al., 1986) and antihypertensive treatment is associated with a lower incidence of dementia in elderly people with isolated systolic hypertension (Forette et al., 1998). Aggressive treatment of hypertension may be unreasonable, especially in patients with severe dementia. A review by Harrison and colleagues (2016) concluded that, overall, there was no good evidence of benefit or harm from treatment for hypertension in people with dementia. Clinicians

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should therefore consider patient preferences, possibly assess further using ambulatory monitoring, and consider deprescribing, especially if there are side-effects.

The elevated incidence of stroke in patients with atrial fibrillation (AF) explains the relationship between AF and the development of VaD (Alonso and Arenas de Larriva, 2016). AF is associated with at least a doubling of stroke risk and the effects of stroke on cognitive function are well established (Gerelick et al., 2011). AF also more than doubles the risk of silent cerebral infarction independent of stroke (Kalantarian et al., 2014) and the presence of silent cerebral infarcts is a risk factor for dementia (Vermeer et al., 2003).

Guidelines are clear in recommending anticoagulant and antiplatelet drugs that can reduce the risk of stroke for most individuals with AF. A recent analysis comparing the risk of dementia in people with AF using warfarin versus non-vitamin K oral anticoagulants (NOACs) reported a lower risk of dementia among NOAC users (Jacobs et al., 2016). The four NOACs licensed in the UK (apixaban, dabigatran etexilate, edoxaban, and rivaroxaban) are all recommended by NICE as an option for prevention of stroke and systemic embolism in people with non-valvular AF (NICE, 2016), although dabigatran is the only NOAC with a specific reversing agent (idarucizumab) for use in an emergency. Older people with AF have the lowest frequency of anticoagulant use and dementia appears to be a significant independent determinant of non-treatment with either aspirin or warfarin for the prevention of recurrent stroke (Moroney et al., 1999).

There may be reluctance to use warfarin where compliance may be a problem and NOACs may be a simpler and potentially safer option. It is important to take into account a patient's overall situation when deciding whether the benefits of anticoagulation outweigh any risks: age alone should not be the deciding factor. If necessary, it may be safer though less effective to select alternatives such as aspirin, 75–300mg/day, or another antiplatelet drug, e.g. clopidogrel.

Antidementia drug treatment for VaD

Several clinical trials in VaD have been conducted with the drugs currently licensed for AD. A meta-analysis by Kavirajan and Schneider (2007) reviewed all VaD placebo-controlled clinical trials of donepezil, rivastigmine, galantamine, and memantine. There were small benefits of uncertain significance in cognition but there was significant heterogeneity of the patients that made generalizations about efficacy difficult. The evidence indicates that neither AChEIs nor memantine should be prescribed for people with VaD, although those with mixed VaD and AD may benefit (O'Brien et al., 2017).

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Other dementias

No specific antidementia treatments are licensed for use in other dementias such as frontotemporal dementia (FTD). Classification of FTD is becoming more complex and the different clinical syndromes may ultimately reveal a variety of underlying pathology, including AD. AD pathology may be seen in 25% of cases of non-fluent/agrammatic primary progressive aphasia (PPA), 25% of cases of semantic variant PPA, and 50% of the logopenic variant of PPA (Grossman, 2012). It would seem reasonable that the sub-set of FTD with underlying AD pathology might respond to AChEIs or memantine, although there are no formal trials confirming this and worsening of behavioural symptoms in FTD by AChEIs has been reported (Mendez et al., 2007). In the logopenic variant of PPA and another condition, posterior cortical atrophy, which are both thought to be atypical variants of AD (Gorno-Tempini et al., 2008; Mendez et al., 2002), it would potentially be worth trying AChEIs or memantine.

There is little evidence for the efficacy of AChEIs or memantine in other important causes of dementia, e.g. corticobasal degeneration, Huntington's disease, and prion disease; in progressive supranuclear palsy, clinical trial data does not support the use of either AChEIs or coenzyme Q (O'Brien et al., 2017).

There have been limited formal trials of drug treatment for people with Down syndrome and AD. There were no trials of rivastigmine or galantamine but one randomized controlled trial with donepezil, and reported as part of a Cochrane review (Mohan et al., 2009), showed a modest non-statistically significant trend in favour of those able to tolerate donepezil treatment. Memantine does not appear to be effective for people with dementia in Down's syndrome (Hanney et al., 2012).

Other putative antidementia therapies

Numerous agents with a variety of properties have been suggested as possible treatments for dementia. Where there have been trials, they have mainly been in AD. However, for no other treatments has adequate evidence emerged to date for them to be part of routine practice. Some examples are discussed in this section. Other treatments that have been considered include statins, anti-inflammatory drugs, and vitamin E.

Ginkgo biloba

There is still considerable controversy about the use and value of Ginkgo biloba extracts. The extracts contain many agents, including flavonoids, terpenoids (including several ginkgolides that are unique to the ginkgo tree), and organic acids. A Cochrane review (Birks and Grimley Evans, 2009) noted that ginkgo appears to be safe with no excess side effects compared with placebo, but many early trials used unsatisfactory methods with small numbers of subjects and publication bias could not be excluded. Overall, the evidence that it has predictable and clinically significant benefits for people with dementia or AD is inconsistent and

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unreliable. Three other studies have now been reported, one examining people with dementia and two primary prevention studies (O'Brien et al., 2017). A study in subjects with dementia and neuropsychiatric features found no additional benefit from ginkgo added to donepezil. In the primary prevention studies, ginkgo did not prevent the development of dementia or AD but there appeared to be an increased risk of stroke and transient ischaemic attack in the ginkgo treated groups (O'Brien et al., 2017); concerns have been expressed previously about possible bleeding complications with ginkgo that are probably uncommon but possibly linked to antagonism of platelet-activating factor. People taking anticoagulants, antiplatelet agents, or with a bleeding diathesis should be especially cautious about taking ginkgo.

Folic acid and B vitamins

Folate is an essential dietary element and low plasma and red cell folate levels lead to increases in plasma total homocysteine, which is a risk factor for brain atrophy, cognitive impairment, and dementia. Plasma homocysteine can be lowered by dietary administration of B vitamins (folic acid and vitamin B₁₂). A Cochrane review (Malouf and Grimley Evans, 2008) concluded that there was no evidence that folic acid with or without vitamin B₁₂ improved cognitive function in unselected elderly people with or without dementia. Since this review, one 18-month study of high-dose folic acid, vitamin B₁₂, and vitamin B₆ involving 409 subjects with mild to moderate AD (MMSE 14-26) and normal plasma homocysteine levels has been reported (Aisen et al., 2008). No benefits on cognition were seen in the intervention group but there was an unexpected increase in depression. Another study (Smith et al., 2010) in subjects with MCI showed that plasma concentrations of homocysteine could be lowered by high-dose folic acid, vitamin B₆, and vitamin B₁₂ given over 24 months and found evidence that this slowed the progression of brain atrophy. Further research is needed to confirm this result and to see whether similar benefits could be seen in people with AD. On current evidence, neither vitamin B₁₂ nor folate, either singly or in combination, can be recommended as treatment for dementia (O'Brien et al., 2017).

Souvenaid

Souvenaid is a nutritional supplement or medical food, containing vitamins and trace elements such as selenium, marketed for the dietary management of early AD. Its components are intended to provide neuroprotection by targeting disease processes in early Alzheimer's disease. There is type II evidence from mainly small, non-replicated randomized controlled trials indicating possible benefits on cognition but the effects are variable between studies and no effect has been shown on global outcomes. A randomized controlled trial of Souvenaid involving over 300 participants with prodromal AD (MMSE > 24) showed no benefit compared with placebo (Soininen et al., 2017). At present, this

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supplement is not recommended unless further evidence becomes available (O'Brien et al., 2017).

Management of non-cognitive symptoms

At some time in the course of their disease, almost all people with dementia will develop one or more non-cognitive symptoms in the form of BPSD (behavioural and psychological symptoms of dementia), which include affective syndromes (depression, anxiety, and irritability), apathy, agitation, aggression, psychosis (delusions and hallucinations), disorders of sleep, wandering, and a variety of inappropriate behaviours (Kales, et al., 2015). BPSD are a complex, heterogeneous group of phenomena that have both a basis in brain disease (Sultzer et al., 2003) and also often represent expressions of distress or attempts at communication by the person with dementia. BPSD cause distress to the individual with dementia, and add considerably to the stresses experienced by family and professional carers and can result in serious risks to the person and others. They are also associated with earlier institutionalization, higher costs, and mortality (Habermann et al., 2009; Herrmann et al., 2006).

Good practice recommendations such as the NICE dementia guideline (2018) recommend nonpharmacological interventions as the first line approach for BPSD and emphasise the importance of assessing pain and other medical conditions, which can often precipitate the development of these problems.

Despite the fact that many of these symptoms may improve or change over a period of a few weeks, pharmacological interventions have often been used as a first line treatment. In particular, there has been concern about the excessive use of antipsychotic drugs for the management of BPSD. This was highlighted by Banerjee (2009) in a report to the UK Department of Health that estimated that at least 180,000 people with dementia were being prescribed antipsychotics each year in the UK. Banerjee estimated that this led to an extra 1,800 deaths a year in the UK, together with an additional 1,620 cerebrovascular adverse events (about half of which are severe). Consequently, official guidelines and regulatory bodies have warned about the risks of these drugs in people with dementia; for example, NICE (2018) recommends that antipsychotics should only be offered to people who are at risk of harming themselves or experiencing agitation, hallucinations, and delusions that are causing them severe distress.

Use of cholinesterase inhibitors or memantine for BPSD

There have been more than 30 randomized controlled trials, with follow-up over 6–12 months, with AChEIs. However, few of these have specifically looked at people with BPSD, particularly clinically relevant agitation. Evidence from these trials suggests an overall effect on neuropsychiatric symptoms over six months, but the main benefits are probably for anxiety and apathy, rather than agitation and aggression

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(Ballard et al., 2009). In the 12-week CALM-AD trial (Howard et al., 2007) donepezil was not more effective than placebo in treating agitation in patients with AD.

Memantine seemed to be a promising treatment for BPSD, based on the main clinical trials, which appeared to show a benefit in reduced irritability, lability, agitation, aggression, and psychosis (Ballard et al., 2009). Clinically, it does seem that memantine may damp down or reduce the appearance of agitation and it has been used by clinicians for this purpose. One trial of memantine in patients with clinically significant agitation from care homes or hospitals did not show improvement (Fox et al., 2012), but it was significantly better than placebo for cognition. The authors commented that it still remains to be determined whether memantine has a role in milder degrees of agitation in AD.

Agitation, aggression, and psychosis

It is important to look for causes of agitation and this has been confirmed in a study that demonstrated that effective management of pain significantly reduced agitation in residents of nursing homes with moderate to severe dementia (Husebo et al., 2011). Paracetamol 1g up to four times per day is a suitable and safe option.

One study (Porsteinsson et al., 2014) assessing the selective serotonin reuptake inhibitor (SSRI) citalopram in people with dementia and clinically significant agitation demonstrated significant improvement over placebo on several clinical measures, including clinical global impression of change and reduced carer distress, but citalopram must be used with caution in people over 65 years (see Depression).

Antipsychotics

Risperidone is the only antipsychotic specifically licensed for use in dementia in Europe and Canada, but not in the US, and only for short-term (up to six weeks) treatment of persistent aggression in moderate to severe AD unresponsive to nonpharmacological approaches and when there is risk of harm to the patient or others. The starting dose should be 0.25mg twice daily, increasing gradually to a maximum dose of 1mg twice daily. There are several alternative antipsychotic drugs, but the evidence for their efficacy is limited and the risks are great (Kales et al., 2015). It is worth emphasizing that patients with DLB may show severe sensitivity to neuroleptic drugs such as the atypical antipsychotics, and fatal reactions have occurred (McKeith et al., 1992).

Depression

Evidence about the potential benefits of antidepressants for treating depression in the context of pre-existing dementia has been provided by two large trials. The DIADS-2 study in the US compared sertraline 100mg (N=67) with placebo (N=64) in depression in AD and found no significant difference in symptom change or response or remission rates, but did find

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an increase in adverse events on sertraline (Rosenberg et al., 2010), and that the evidence does not support the use of SSRIs in depression in AD. The SADD Study in the UK reported similar findings in a larger sample of 326 subjects. In this study a broader and more representative definition of dementia was used and subjects randomised to placebo (N=111), sertraline (N=107), or mirtazapine (N=108) (Banerjee et al., 2011). Sertraline was not better than placebo and was associated with more adverse events, and mirtazapine was no better than placebo on any outcomes. These two large studies and a recent Cochrane review (Dudas et al., 2018) demonstrate that, contrary to previous belief, monoamine-based antidepressants are not generally effective in depression in dementia. As is typical of clinical trials, the most severely ill patients were not assessed; for severe depression pharmacological treatment may be appropriate, for example, with an SSRI such as citalopram 10mg daily, increasing to a maximum of 20mg per day. Higher doses should not be used in patients older than 65 years because of an association of the drug with dose-dependent QT interval prolongation (MHRA, 2011).

Sleep disturbance

Non-drug sleep hygiene measures are always preferable but treatment with medicines is often used to try and improve sleep in people with dementia. There is a lack of evidence to guide such treatment. A recent Cochrane review (McCleery et al., 2016) noted no randomized clinical trials of benzodiazepine or non-benzodiazepine hypnotics and no evidence that sleep problems were helped either by melatonin (up to 10mg) in moderate to severe AD or ramelteon in mild to moderate AD. There was some limited evidence of benefit with low dose (50mg) trazodone.

Overview of pharmacological treatment for people with dementia

Box 35.1 provides a summary of the main aspects of pharmacological treatments for dementia discussed thus far in this chapter.

Box 35.1 Summary overview of pharmacological treatment for people with dementia

- Assess the patient with a possible dementing disorder carefully, including a formal screening instrument (e.g. MMSE, sMMSE, MoCA)
- Establish that the patient has dementia
- Establish the most likely type of dementia

If Alzheimer's disease:

- consider oral AChEIs (donepezil, galantamine, or rivastigmine) and explain goals of treatment (some early benefits potentially

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but stabilization or less than expected decline more likely). Assess cognition (e.g. MMSE, MoCA). Titrate to maximum dose if possible according to side effects and benefits

- if problems with first AChEI, consider switching to another AChEI (consider transdermal rivastigmine) or memantine
- if AChEIs poorly tolerated or contraindicated, consider memantine
- as disease progresses, consider switching to memantine or adding memantine to the AChEI, particularly if the patient is developing agitation
- monitor the patient's progress regularly (approximately six-monthly)
- if stopping drug treatment, consider dose *reduction* rather than complete withdrawal, and be aware that the patient may deteriorate and medication may need to be restarted

If dementia with Lewy bodies:

- consider L-dopa for parkinsonian symptoms with careful monitoring for emergent psychosis
- consider AChEIs (and possibly memantine), especially for visual hallucinations
- do *not* use neuroleptics

If vascular dementia:

- consider sources of emboli (e.g. carotid disease, AF)
- if atrial fibrillation, consider anticoagulation
- give low-dose aspirin (if contraindicated, consider clopidogrel)
- ensure other relevant conditions (e.g. hypertension, diabetes) are being managed appropriately

AChEI—acetylcholinesterase inhibitor; MMSE—Mini-Mental State Examination; sMMSE—Standardized Mini-Mental State Examination; MoCA—Montreal Cognitive Assessment.

Prospects for future treatment

Unfortunately, no new drugs have been licensed for the treatment of dementia since memantine in 2002; the search for more effective and potentially disease-modifying drugs continues. There have been several new initiatives to try and increase the chances of success, including several international partnerships, such as the Global Alzheimer's Platform (GAP, mainly North America); the European Prevention of

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Alzheimer's Disease Consortium (EPAD); and the Dementias Platform UK (DPUK). These are private-public collaborations, aimed at developing new treatments but also establishing cohorts of well-characterized potential participants.

Recently an international political agenda has developed with the ambition to identify 'a cure, or a disease-modifying therapy, for dementia by 2025' outlined at the G8 dementia summit in December 2013 (Department of Health and Social Care, 2014) and in the US National Plan to address Alzheimer's disease 'to prevent and effectively treat AD by 2025' (US Department of Health and Social Services, 2013). Given the 2025 target, under current conditions, only drugs already in phase II or later will have any chance of being approved by 2025 (Cummings et al., 2016). Cummings and colleagues (2016) also identified several factors that could reduce the time and risk of AD drug development, such as improved trial design; better trial infrastructure; disease registries of well-characterized participant cohorts; validated biomarkers for disease detection, assessing risk, monitoring disease progression, and prediction of disease response; more sensitive clinical assessment tools; and faster regulatory review.

Many compounds have been investigated for AD with numerous unsuccessful or failed trials leading to discussion about the reasons for this. Most approaches have focused on the amyloid hypothesis and compounds that in some way affect the production, deposition, or removal of the toxic 42-amino acid peptide amyloid-beta (A β). For example, there has been much interest in the possibility that monoclonal antibodies that bind to A β might be effective treatments for AD. However, trials of solanezumab in mild to moderate (Doody et al., 2014) and mild AD (Honig et al., 2018) failed to show any significant benefit. Aducanumab failed to meet its primary end points in several phase 3 trials on interim futility analyses, but interestingly a re-analysis by its manufacturer, Biogen which included additional data found benefits. At time of writing, this has lead the company to apply for regulatory approval for the use of aducanumab in the United States.

Deposition of A β within the brain begins many years before the clinical manifestations of AD are apparent, so it may be that such drugs need to be given earlier in the AD process, either when symptoms are mild (MCI or prodromal AD) or possibly even before symptoms begin (asymptomatic preclinical AD). Increasingly, biomarkers such as CSF amyloid and tau, and PET amyloid and tau functional imaging are being used in order to detect underlying AD pathology earlier, and trials in such individuals may be more effective. Other approaches are also important, such as targeting tau deposition in neurofibrillary tangles, as well as other aspects of the neurodegenerative disease process, including neuroprotective, anti-inflammatory, and metabolic approaches.

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Currently available licensed drug treatments are generally only considered to be symptomatic therapies with no significant effect on halting or reversing the underlying disease process. However, a recent study with donepezil in people with suspected prodromal AD demonstrated a 45% reduction of the rate of hippocampal atrophy following one year of treatment compared with placebo, which is not something that would generally be expected in a purely symptomatic treatment (Dubois et al., 2015). The boundary between symptomatic and disease-modifying therapies may therefore be somewhat blurred, particularly in identifying the differences clinically. Current treatments certainly may change the disease course by delaying deterioration and, for example, entry to nursing homes (Lopez et al., 2009) without necessarily changing the disease itself.

It will be a significant hurdle for new therapies to be accepted as disease modifying. Such drugs will need to show clinical efficacy over a sustained period of time (12–18 months minimum), including possibly a change in the slope of decline and delay in reaching particular disease milestones, such as a change in disease severity (using a measure such as the Clinical Dementia Rating Scale), the transition from prodromal AD to Alzheimer's dementia, or loss of independence. Interestingly, if aducanumab is approved, then this would be counterflow to these expectations. Regardless, there are likely to be considerable challenges with administration of these drugs, as they may need initial monitoring for safety with MRI scans and may involve regular injections or infusions; cost-effectiveness will undoubtedly also be a consideration if they are to achieve widespread usage. However, such advances in treatment for people with AD and other dementias are essential, given the predicted increase worldwide in the numbers of older people and people with dementia.

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Management of dementia

Chapter: Management of dementia

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Introduction

An estimated 50 million people are living with dementia worldwide in 2017 (Prince et al., 2015) and this number will reach 135 million by 2050. The worldwide costs of dementia are also increasing and it has been reported that dementia will be a trillion-dollar disease by 2018 (Prince et al., 2016). The majority of this cost is due to social care, as, despite substantial effort by the pharmaceutical industry, the prospect of finding a cure for dementia is not imminent (Cummings et al., 2017). Much of the social cost is borne by the families, as they are often unable to access assistance from agencies that are struggling to cope with demand (Bourne, 2007). For this reason, the management of dementia should focus on supporting and developing the care provided by family members and carers in the community, because their education and enablement will help to optimise the quality of life for people with dementia.

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Dementia encompasses a group of neurodegenerative disorders that are characterized by progressive loss of cognitive function and ability to perform activities of daily living (ADLs), and that can be accompanied by neuropsychiatric symptoms and challenging behaviours of varying type and severity. Dementia changes the way people with the disease interact with the world around them, as well as how the world (including friends, families, carers, communities, and services) responds to them. The social model of dementia (Kitwood and Bredin, 1997) helped to redefine dementia as a disability, produced by social exclusion, mostly due to fear and lack of understanding. The person-centred model of care that emerged in the 1980s promoted the understanding of the person behind the dementia, and the context in which he/she lives. Thus, the management of dementia is not limited to the management of individuals and the disease, but must also include their personal, physical, social, and cultural environments. This means that modern dementia services must understand the management issues in a variety of sociocultural settings, and also identify the specific needs of people with dementia and their carers, regardless of their age, class, ethnicity, religion, sexuality, or comorbid disability. These principles are reflected in the UK guidelines for dementia care produced by the National Institute for Health and Clinical Excellence and the Social Care Institute for Excellence (NICE-SCIE, 2006), which emphasize the importance of services being person-centred, relationship-centred, autonomy-centred, and providing good-quality, evidence-based care. These guidelines have been used to shape services in UK. More recently, the 2017 Lancet Commission on Dementia (Livingston et al., 2017) has collated the latest evidence for prevention, management, and care of dementia. We have therefore used both of these documents as reference sources to update this chapter on the management of dementia.

The dementias are progressive disorders and presentations change over time. People with dementia also have different needs at different stages of the disease, and their management needs (and those of their carers and environments) will vary accordingly. This chapter concentrates on the assessment and management of people with dementia in the early and later stages of the disorder. At both stages we consider engagement, autonomy, respect, protection, and ethical issues, as well as describe the clinical and psychosocial aspects of treatment. The emphasis is on the broader principles of management, which apply to people with dementia of any aetiology, their families, carers, and communities, and take into account the different settings in which they may present. More specific treatments are covered in other chapters (e.g. Chapters 13–19 and Chapter 35).

Early dementia

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Presentation of early dementia

People with early dementia may present in a number of different ways. They may notice changes in themselves and self-refer to health professionals in primary care, or their family members may become concerned and suggest that they have an assessment. Health and social care professionals sometimes suspect cognitive impairment in people referred to them for other reasons, and may then suggest a clinical assessment for dementia. Irrespective of the location and presentation, all people with suspected dementia and their families will benefit from a full and comprehensive diagnostic assessment and evaluation of their needs. Until recently, assessment and management of dementia in the UK was mostly conducted within specialist memory services (NICE-SCIE, 2006), which were generally run by mental health services (Department of Health, 2009). Over the past five years, there has been a global shift towards primary care services taking the lead in screening, assessment, diagnosis, and management of dementia. Evidence is emerging that, given the right level of training and resources, these services could provide comprehensive care for patients with dementia (Spenceley et al., 2015).

Assessment of early dementia

Assessment of early dementia includes a detailed description of the presenting problems, psychiatric and medical history, current medication, functional ability, living situation, the ability of significant others to provide care, plus a physical examination, mental state examination, and assessment of the risks of harm to self and others. If consent is given, it is useful to corroborate the history with a member of the family or someone who knows the person well, as even in mild dementia there may be subtle changes in memory, behaviour, or personality that the person with dementia has not noticed. Although people with dementia and their carers are typically seen together, it is also valuable to see them separately to allow both the opportunity to discuss any confidential matters. If the person does not speak English it is good practice to use an approved interpreter, rather than a member of the person's family, so that relatives' personal opinions do not overly influence the assessment (Moriarty et al., 2011). In the UK, the carers of people with dementia have the right to receive an assessment of their own needs, as set out in the Carers and Disabled Children Act 2000 and the Carers (Equal Opportunities) Act 2004.

Appropriate investigations help to confirm the diagnosis and aetiology of dementia, which enables a more accurate prediction of the natural course of the disease; this in turn facilitates information sharing, forward planning, and individually tailored management packages for people with dementia and their families. NICE-SCIE guidelines (2006) recommend that a basic dementia screen should be performed at the initial presentation, including routine haematology, inflammatory markers, serum B₁₂ and folate, and tests for electrolytes, calcium, glucose, liver,

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renal, and thyroid function. A urine sample is collected if a urinary tract infection is suspected. Testing for syphilis and HIV is also carried out if indicated as appropriate by the clinical history. Other physical investigations that help with the diagnosis and the aetiology or subtype of the dementia include neuroradiological imaging, both structural, e.g. magnetic resonance imaging (MRI) or computed tomography (CT), and functional, e.g. single-photon emission computed tomography (SPECT). Sometimes electroencephalography or cerebrospinal fluid examination can be helpful in elucidating the diagnosis. Molecular imaging techniques, amyloid, and tau-labelled positron emission tomography (PET) scans are not yet widely available in UK clinical services.

Brief tests such as the Mini Mental State Examination (MMSE) (Folstein et al., 1975) and the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) are often used to assess cognitive function. In early dementia these tests can be misleading, as performance is affected by educational and sociocultural background, by functional illness (especially depression), and by non-Alzheimer's dementias. In frontotemporal dementia, changes in behaviour and personality often occur before cognitive decline, and in Lewy body dementia (LBD), memory is often initially spared. Thus, in early dementia, a more sensitive neuropsychological assessment is often required, e.g. the Addenbrookes Cognitive Examination-III (ACE-III) (Hsieh et al., 2013). Alternatively, a complete neuropsychological test battery can be administered, which evaluates specific domains of cognitive function, such as attention and concentration, orientation, short- and long-term memory, praxis, language, and executive function. Combined with the clinical findings and other investigations, a neuropsychological profile is generated that may help to identify a particular subtype of dementia.

The assessment of dementia is discussed in more detail in Chapter 9, Chapter 10, Chapter 23, and Chapter 28.

Management of early dementia

The assessment of the person with dementia identifies the unique circumstances and needs for that person and their family in order to create an individually tailored care plan to meet those needs. Once a diagnosis has been made and a management plan produced, most dementia will be managed by the family, assisted by primary care and social care services. The role of the dementia specialist is increasingly to educate and offer expert advice to workers in primary care, secondary care, social care, and residential care settings, in order to provide optimal care for the person with dementia (Department of Health and Care Services Improvement Partnership, 2005).

The main management tasks in early dementia of any aetiology are i) providing person-centred care, ii) disclosing the diagnosis, iii) optimizing

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quality of life in the present, iv) interventions for cognitive symptoms of dementia, and v) planning for the future.

Person-centred care

Person-centred care has become the cornerstone of the management of dementia. It upholds the idea that, throughout the course of their illness, people with dementia should remain valued as individual human beings with their own personal perspective on the world; they will require authentic and respectful communication from the people around them at all times (Kitwood, 1997). In early dementia, this approach requires an active process of respecting the person with dementia's right to autonomy in decision-making, while also maintaining duty of care. In the UK there is now a legal framework in place— the Mental Capacity Act (2005), which was implemented in 2007—that helps guide health and social care professionals. Under the Mental Capacity Act, people are assumed to have capacity to make decisions about their care until proved otherwise, and even if a person does not have capacity, then a decision made in that person's best interest must take into account his or her past and current preferences on the subject. In early dementia, the principle of respecting autonomy applies to diagnostic assessment, confidentiality, gaining consent to speak with family members, requesting physical investigations, disclosing the diagnosis, starting treatment with drugs, future planning, collaborative care, and more complex decisions, such as who should take responsibility when a person is no longer able to manage his or her finances. The majority of people with early dementia are likely to retain capacity to make decisions in most areas, but service providers can sometimes assume otherwise and undermine the autonomy of people with dementia. Hence health and social care providers are advised to support training of their employees regarding autonomy and capacity to consent in people with dementia, to ensure that they respect their legal and human rights (Department of Health, 2009).

Engaging the family of the person with dementia in collaborative planning for the present and for the future is vital. It is important to remember that consent should be obtained from the person with dementia to have the family member involved (NICE-SCIE, 2006), and, as the person's initial decision may change, requesting consent is a process that should be repeated frequently.

Disclosing the diagnosis

There is a common concern that the experience of diagnosis disclosure will be distressing for people with dementia, their family members, and for the healthcare professionals involved. Some practitioners are reluctant to impart a diagnosis for a progressive terminal disease with as yet no effective cure and uncertain prognosis (Robinson et al., 2011). However, most people with dementia wish to know their diagnosis (Pinner and Bouman, 2003), and disclosure may even reduce anxiety (Mormont et al., 2014). People with dementia and their families require adequate time

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to discuss the diagnosis and its implications. The disclosure of the diagnosis of dementia is best conducted over a series of contacts, rather than in a single interview, because patients and carers may not retain information about the diagnosis after the first disclosure. Eight key behaviours have been identified as 'best practice': preparing for disclosure, integrating family members, exploring the patient's perspective, disclosing the diagnosis, responding to patient reactions, focusing on quality of life and wellbeing, planning for the future, and communicating effectively (Lecouturier et al., 2008). Written information about the signs, symptoms, course, prognosis, and treatments for dementia is important, as is signposting people to local care and support services, financial advice, legal advice, and advocacy (NICE- SCIE, 2006). There are particularly good resources available online, e.g. Alzheimer's Society (<http://www.alzheimers.org.uk>).

Optimizing quality of life in early dementia

The main goal of management at this stage is to optimise the person with dementia's function and quality of life by identifying and treating any potentially reversible factors (physical, psychological, environmental, and/or sociocultural) that might have an adverse impact.

Reversible factors—physical

Although dementia is a progressive disorder, it usually presents in later life when there are many other factors—biological and non-biological—that affect the optimal function of both the brain and the body. The saying 'what's good for the body is good for the brain' is useful guidance to people with dementia. There is increasing evidence (Livingston et al., 2017)) that the benefits of good nutrition, regular sleep, exercise, reducing alcohol and tobacco intake, and keeping to a weekly and daily routine are likely to reduce the impact of the disease. More specific health interventions may include controlling high blood pressure, dyslipidaemia, diabetes, vascular risk factors, and managing chronic illnesses, e.g. osteoporosis and sensory impairment, all of which can also exacerbate the extent of cognitive and functional impairment in people with early dementia. Alcohol and substance use disorders should be considered as they are increasingly common in older people (Kuerbis et al., 2014) and are likely to worsen any cognitive impairment seen in an underlying dementia (Royal College of Psychiatrists, 2005).

Physical factors may also cause a delirium in a person with early dementia. Delirium can be thought of as 'acute brain failure' in response to a noxious insult (Inouye et al., 2014), which is most often physical but may also be psychological, social, and/or environmental. Common causes of delirium are infection (respiratory and urinary tract), heart failure, electrolyte or metabolic imbalance, and untreated pain. Many prescribed drugs can also worsen cognitive impairment, particularly those with anticholinergic side effects (e.g. tricyclic antidepressants and drugs prescribed for urinary frequency and bladder instability) as they may

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exacerbate the symptoms caused by the cholinergic deficit that is a feature of most dementing illnesses. Other medications that commonly cause confusion are opioids (including tramadol, fentanyl, and buprenorphine), but severe pain can also worsen cognitive impairment, so balancing the benefits versus the harm of potent analgesics can be challenging. If delirium is present, the severity of the underlying dementia may be over-diagnosed, so it is essential to obtain from someone who knows the patient well any collateral information about the level of cognitive function prior to the current illness. Recent sudden deterioration almost always indicates a delirium. In the UK, NICE guidelines recommend that all cases of previously undiagnosed dementia in the acute hospital be referred to a hospital mental health liaison service for a full assessment (Department of Health, 2009). The service will usually recommend prompt treatment of the underlying physical disorder, a swift discharge from hospital, with intermediate care if required, followed by a full assessment by the local memory service once the condition has stabilized. The aim of this approach is to return the patient to a familiar environment as quickly as possible, since hospital admission in dementia is associated with adverse outcomes, including increased length of stay, institutionalization, and mortality (Royal College of Psychiatrists, 2005; Sampson et al., 2009).

Reversible factors—psychological

Symptoms of depression and anxiety may arise secondary to the patient's insight into their diagnosis and concern about the changes associated with the early stages of dementia, or in response to the change in other people's behaviour towards them. NICE guidelines recommend that people with early dementia of all types should be given the opportunity to have post-diagnostic counselling to explore what the diagnosis means to them and to develop coping strategies (NICE-SCIE, 2006). In practice this rarely happened in hard-pressed services, but following the 2012 Prime Minister's Dementia Challenge there has been increased interest in providing good quality post-diagnostic support for both the person living with dementia and their families and a wide range of psychosocial interventions are now available (Guss et al., 2014).

Some people with early dementia will have a comorbid depressive illness. The prevalence of depression in people with dementia is approximately 20%, with the annual incidence rates of major and minor depression being reported as 10% and 30%, respectively (Ballard et al., 1996). People with early dementia who have a coexisting depressive illness are likely to present with characteristic symptoms including low mood, tearfulness, insomnia, lack of enjoyment, reduced motivation, and poor appetite, but the syndrome may additionally worsen their cognitive function and ADLs. As depression can present with similar symptoms to early dementia, a new diagnosis of dementia should usually be suspended until after the depressive illness is successfully treated. Recently, Petersen and colleagues (2017) reported that major depression in people with mild dementia more than doubled mortality rate at three-year follow-

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up. Given that depression is potentially treatable, it is important to assess for depressive symptoms and be proactive in its treatment. As there is frequently an overlap of physical symptoms, e.g. apathy and fatigue, between depression and dementia, it is important to identify target non-somatic symptoms, e.g. anhedonia and guilt, which can be monitored to ensure reduction in symptoms over time. Rating scales for depression, e.g. the 15-item Geriatric Depression Scale (GDS-15) (Sheikh and Yesavage, 1986), show validity for use in people with early dementia (Burke et al., 1989), and can be used to help assess the severity of depression prior to treatment and to examine treatment response.

Nonpharmacological interventions for depression in early dementia are the mainstay of treatment and include maintaining pleasurable activities, addressing relationship and environmental difficulties, exercise, as well as psychoeducation and psychological support. More specific psychological treatments, such as cognitive behavioural therapy for depression, are also effective in early dementia (Orgeta et al., 2014). There are insufficient high-quality RCTs to assess the efficacy of antidepressant medications in people with dementia (Orgeta et al., 2017) but they are effective for the treatment of depression in older people without dementia (Mottram et al., 2006) and should be considered as part of the management. Sequenced treatment plans are recommended in various guidelines (NICE, 2009). Usually a selective serotonin reuptake inhibitor (SSRI) is used first-line. If there is no response to the first class of antidepressant, then another from the same or a different class should be tried; or, if there is a partial response, then augmentation with another antidepressant can be used, e.g. adding mirtazapine to an SSRI. Robust treatment strategies are more likely to lead to successful outcomes and lessen therapeutic nihilism. If there is a past history of depressive illness, a previous good response to antidepressant medication usually predicts future response and it makes sense to try successful treatments again. Older patients on long-term antidepressant therapy may have taken tricyclic antidepressants for many years. As the anticholinergic side effects are likely to worsen the confusion seen in dementia, it may be necessary to switch the patient to either another tricyclic antidepressant with fewer anticholinergic side effects (e.g. lofepramine) or an antidepressant from an alternative class, such as an SSRI. Close monitoring is required as there are considerable risks associated with antidepressants in older people, including anticholinergic side effects, cardiotoxicity, gastrointestinal bleeding, hyponatraemia, falls, and fractures (Coupland et al., 2011). As with treatment of depression in any other patient group, the patient with dementia should be kept on a maintenance treatment regime using the drug and dose that resulted in effective remission of symptoms: 'the dose that gets you well, keeps you well'.

Occasionally, people with early dementia present with psychotic symptoms. People with psychosis may believe that people are trying to harm or steal from them. It should be remembered that sometimes the

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belief is true, but most often these delusions are the result of people with dementia trying to make sense of their world: if they are unable to find familiar items or money (often misplaced due to forgetfulness) they may conclude that they have been stolen. Other people may present with hallucinations, which are usually visual, well-formed, and detailed, and may be recognized as unreal and even pleasant by the person. Less commonly, in early dementia the emergence of hallucinations may be part of the syndrome associated with LBD (McKeith et al., 1996). If LBD is suspected, it is useful to enquire about other symptoms, such as fluctuating cognition, visual hallucinations, REM sleep disorder, parkinsonian symptoms, and sensitivity to dopamine antagonists, e.g. neuroleptics, but also antiemetics such as metoclopramide. The treatment of psychosis in dementia is discussed in more detail later in the chapter.

Reversible factors—environmental and sociocultural

In early dementia most ADLs remain intact, although there may be subtle changes in managing finances or remembering to take medication. The opinion of an informant who knows the patient well is useful, as people with dementia may not always have insight into their difficulties. An assessment carried out in the person's home creates the opportunity to make a quick evaluation of any environmental risks (e.g. out-of-date food or fire hazards, e.g. burnt saucepans) and the need for any aids, equipment, or adaptations in the house. Advice regarding enhancing ADLs can be sought from an occupational therapist and/or physiotherapist. Environmental modifications inside and outside the home may be required, e.g. the instalment of stair rails or shower facilities. Assistive technology can also help promote independence, e.g. an automatic pill dispenser can remind people with dementia when it is time to take their medication that might otherwise have been forgotten, particularly if they live alone and have no other means of being reminded. In the era of smart phones, smart homes, and the growing use of information and robotic technologies, there is increasing interest in the use of assistive technology to support people living in their own homes and to reassure family members about their safety. However, the associated ethical issues should always be considered as the new technology may compromise the person's right to privacy, and may also reduce access to real social contact.

Social care services can be engaged to provide home care and day care that will support independent living at home for as long as possible. People with early dementia may not recognize the extent of their difficulties and will sometimes send away the home care worker who arrives at their house to help them with food preparation, cleaning, or personal care. It is becoming part of the remit of specialist mental health services to educate staff in mainstream services so that they can recognize and provide good-quality care to the increasing number of people that they will see who will have a dementing illness (Department of Health and Care Services Improvement Partnership, 2005).

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The most important sociocultural interventions are those that support the family of people with dementia. Families will provide the majority of the care for the person with dementia, and therefore need to be supported from the beginning. They will face many difficult challenges, including coming to terms with the diagnosis themselves. They will gradually need to take over decision-making and will have to weigh up the balance of autonomy versus risk in the process, which may lead to disagreements and distress. This can happen even at early stages of dementia, with decisions about driving, for example. Carers may have problems looking after their own needs as well as those of the person with dementia. They may admit to frustration, along with verbal and sometimes physical aggression towards the person with dementia. Pre-existing ambivalence in the relationship may make adjustment more difficult and abuse more likely (Homer and Gilleard, 1990). As the disease progresses it has further psychological effects on the carer, in particular on the spouse, who often goes through a grieving process for aspects of his or her partner that disappear, while having to quickly adjust to new aspects that may emerge. It is essential that carers are supported with whatever they are dealing with, and do not feel they have to shoulder the burden alone. If the caregiver is supported to manage the challenges of caregiving, they will benefit, and the person with dementia benefits as well. Specific interventions for carers of people with early dementia include individual and group psychoeducation, peer support groups, support by telephone and via the Internet, training courses, problem-solving, communication courses, and cognitive behavioural therapy (Selwood, 2007). Family therapy has also been shown to be helpful in families of people with dementia, providing a space for stories to be heard and long-standing disputes to be resolved (Gilleard, 1996). Interventions designed to improve carers' mental health need to be individually tailored, rather than generic. Initiatives such as STRategies for RelaTives (START) help caregivers tackle their own particular challenges, plan for the future, and build in relaxation time; the carer leaves with a personalized manual to continue strategies they had found effective (Livingston et al., 2014a). START has been shown to reduce anxiety and depressive symptoms in carers and has been found to be cost-effective in both the short and long term.

Interventions for cognitive symptoms of dementia

The use of acetyl cholinesterase inhibitors in the management of dementia is discussed in Chapter 35 and will not be discussed in detail here. The three main cholinesterase inhibitors, donepezil, rivastigmine, and galantamine, are used in the treatment of Alzheimer's disease dementia and have similar efficacy in improving symptoms of cognition, function, and behaviour (Birks, 2006). Not all people with dementia will respond to treatment with cholinesterase inhibitors but, as it is not possible to predict those that will, all those without contraindications will be offered a trial of treatment. Cholinesterase inhibitors should be continued for people whose dementia has become severe as

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discontinuation results in a cognitive and functional decline, an increased likelihood of emergence of neuropsychiatric symptoms, and doubles the risk of admission to a care home (Howard et al., 2012, 2015). Memantine acts at different receptor sites to the cholinesterase inhibitors; its therapeutic action is thought to arise from blocking N-methyl-D-aspartate (NDMA) receptors, resulting in a neuroprotective effect on the brain. Memantine is well tolerated and confers some benefit on functional and cognitive outcomes in dementia (McShane et al., 2006); in the UK it is recommended for use in people with moderate AD in whom cholinesterase inhibitors are contraindicated or not tolerated due to adverse side effects (NICE, 2011).

There are also several nonpharmacological interventions aimed at improving the cognitive symptoms of early dementia. Cognitive stimulation therapy, a group-based reality orientation therapy, has the strongest evidence for improving cognitive function (Woods, 2012). Other interventions such as cognitive training, reminiscence therapy, validation therapy, and exercise are all helpful in reinforcing positive coping strategies, but most systematic reviews have concluded that there are insufficient robust studies to draw conclusive verdicts about their effectiveness (Livingston et al., 2017).

Planning for the future

Timely diagnosis of dementia allows the person with early dementia to be involved in planning for their future. Typical issues are decisions about stopping driving, financial management and advanced care planning. Decisions regarding driving ability can be a particularly challenging area as it is possibly the most significant issue that affects a person's independence. People with early dementia do not have to automatically give up driving, but even mild stages of dementia can increase the risk of failing a performance-based road test (Chee et al., 2017). A history of accidents or near misses (either given by the patient or by someone who knows them), evidence of executive dysfunction or visuospatial deficits on neuropsychological testing, and the new prescription of psychotropic medication may all affect ability to drive. In the UK, people with dementia are legally obliged (if advised by their doctor) to notify the Driver and Vehicle Licensing Agency (DVLA) and should also inform their motor insurance provider. If the clinician feels they have insufficient information about driving to advise the patient, they can suggest taking a disabled driving assessment at a local centre. In those who can continue to drive, it is sensible to advise that they avoid driving in heavy traffic, at night, or in bad weather and to drive accompanied if possible. Decisions regarding driving must be reviewed regularly, as dementia is a progressive disorder and thus driving ability will change. If the person with dementia refuses to stop driving, then the person's family may need to disable the car, or even involve the police to prevent unsafe driving becoming a hazard to the public.

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People with early dementia may be aware that they are beginning to find it difficult to manage their financial affairs, perhaps not paying their bills on time, or forgetting they have withdrawn money from the bank. They may become vulnerable to financial exploitation, whether due to consumer fraud or undue coercion by people known to them who aim to persuade them to use their assets against their best interests. For these reasons, a key aspect of management at this time is to discuss whom they would like to manage their financial affairs in the future. In the UK, people can make a Lasting Power of Attorney for Property and Financial Affairs (LPA(PFA)), which can either be used as soon as it is registered or when people lose capacity. They may also wish to appoint someone to make decisions about their future health and social care, in which case they can make a separate Lasting Power of Attorney for Health and Welfare (LPA(H&W)). These issues are covered in more detail in Chapter 52 and Chapter 58.

Later dementia

Presentation of later dementia

Some people with dementia do not present until later in the course of the disease. This is commonly because the person providing care for the individual with dementia believes that his/her behaviour is an inevitable part of ageing and is perhaps unaware that help and support are available. Sometimes the caregiver may delay seeking help for fear of the consequences of diagnosis, for example, placement in residential care. In these situations, presentation is often precipitated by a change in the caregiver's circumstances; the caregiver themselves may become too psychologically or physically unwell to be able to provide care any longer. Other people without carers but with fairly advanced dementia continue to live independently in their own homes without help for many years, particularly if they have well-established routines, having lived in the same house for many years, treading well-worn routes to the shops and other facilities in their local area. Likewise, people who have lived in residential care for many years may develop dementia but care staff do not recognize their gradual cognitive and functional decline. In both these scenarios the presentation is usually triggered by a physical, psychosocial, or environmental change in the person with dementia; they are liable to present in crisis or at immediate risk, and are thus more likely to require specialist dementia care from health and/or social care services.

Reasons for referral in later dementia are usually due to behaviours identified as high risk or challenging. These have been described as 'behaviours that challenge', because they are problematic for the people with the behaviour and to the people around them, including families, neighbours, co-residents, and care staff. They are also referred to as the behavioural and psychological symptoms of dementia (BPSD), and, for the sake of convenience, that term will be used here. If people with later dementia still live at home, BPSD may include wandering, leaving the

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front door open, poor hygiene, hoarding, incontinence, self-neglect, weight loss, and allegations about people stealing from them or harming them in some way. If they live in supported accommodation, residential care, or a nursing home, then their behaviours are likely to be those that staff and other residents find difficult to tolerate, and may include screaming, shouting, calling out, wandering, agitation, verbal or physical aggression, inappropriate incontinence, faecal smearing, and inappropriate sexual behaviour. Other symptoms may include delusions, hallucinations, anxiety, depression, apathy, misidentification, and disinhibition. At this stage of dementia, individuals are less likely to have capacity to make decisions about their care and, having little insight into the extent of their difficulties, may refuse help. The ethical issue of intervening in someone's life without their consent, possibly in response to third-party information, often has to be considered in these circumstances. Specialist input from community-based mental health and social care services may be required in the short term, but this should always be a collaborative process, working with families, primary healthcare professionals, social care services, and involving the person with dementia as much as possible in the decision-making process.

Assessment of later dementia

In later dementia it remains essential to carry out a comprehensive assessment of needs, accurately describing the target symptoms, in order to develop a robust management plan. Gathering all the information required can be challenging as people with dementia may not be able to communicate their difficulties easily, so an informant's history becomes increasingly important. If the person with dementia is living in a care home, it is important to bring together the views of both the care home staff and visiting family members or friends, as every perspective will be valuable. Care home staff are able to give details of day-to-day behaviours, but friends and family members are able to bring years of knowledge about the person and his or her usual ways of reacting to events. Involving families and carers in the assessment process has the added benefit of involving them in the management process too.

Physical investigations may be required to confirm the diagnosis and subtype of dementia, and to identify any reversible factors. A diagnosis can help explain patterns of behaviour and predict a treatment response to some pharmacological interventions. However, a person with later-stage dementia may be unable to tolerate having blood tests or neuroimaging, in which case it may be necessary to rely solely on clinical history, mental state examination, and observations from carers.

Assessment of BPSD

The behavioural and psychological symptoms of dementia (BPSD) are a complex group of behaviours that increase in frequency and severity as the dementia progresses (Savva et al., 2009; Brodaty et al., 2015), are strongly associated with carer distress (Black and Almeida, 2004), and

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adverse outcomes such as entry into institutional care (Brodaty et al., 2014) and prolonged length of stay in hospitals (Royal College of Psychiatrists, 2005). Therefore, it is important to assess and treat in order to improve patient and carer outcomes.

Assessment of BPSD requires understanding the behaviour as an attempt by the person to express an unmet need, which may be physical or psychological (Stokes, 2000), rather than as an inevitable (and thus untreatable) feature of later dementia. The behaviour needs to be understood as a method of communication that reflects the interaction between the person with dementia, the care giver, and the environment (Fig. 36.1); the challenge is to understand the communication. Failing to understand the communication, or worse, treating the behaviour as a nuisance, will only result in intensifying the behaviour intended to communicate the unmet need. To understand the behaviour, we need to first understand the individual—their personal and family background, their premorbid personality, their past medical and psychiatric history, their current physical and psychological problems, their communication difficulties in terms of speech and hearing, and their social situation. Second, we need to be able to make accurate and non-judgmental observations of a person's behaviour. The most commonly used approach is the 'ABC' method, in which the context or antecedent (A) of the behaviour is reported, the behaviour (B) itself is described, and then the consequences (C) of the behaviour are observed and documented. The understanding of BPSD depends upon the cooperation of carers, who are often under considerable stress themselves. As most carers have no training, this task can appear overwhelming and often futile. Dementia specialists undertake to enable and empower carers, family members, and significant others in the objective observation of behaviour without adding opinion or judgment. Once information has been gathered about the nature of the behaviours, they can, in the light of what they know about the person's background, create a hypothesis about what the behaviour means in terms of unmet need; after this, a management plan can be initiated, implemented, and evaluated.

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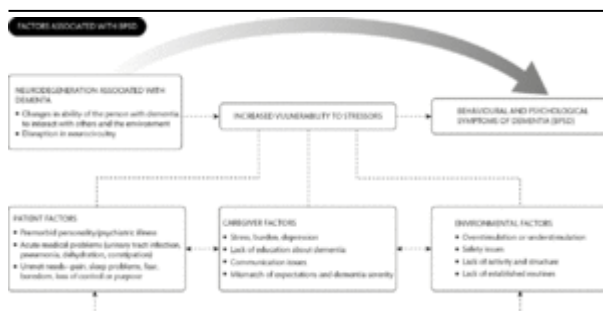


Fig. 36.1

The behaviour needs to be understood as a method of communication that reflects the interaction between the person with dementia, the care giver, and the environment.

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The causes of BPSD, and therefore their management, can be broadly categorized into physical, psychological, social, and environmental factors. Describing the presenting symptoms is essential, as is actively seeking out their possible causes in all of these areas, before starting targeted treatment. Clinicians sometimes use tools such as the Neuropsychiatric Inventory-Questionnaire (Kaufer et al., 2000) to measure the baseline severity and distress caused by behavioural and psychological symptoms of dementia and which can also be used to monitor the response to interventions.

Physical causes of BPSD

As in early dementia, physical and pharmacological factors can have a detrimental effect in later dementia, and these should always be considered in BPSD. Pain, infection, dehydration, constipation, and adverse drug side-effects are all common causes of agitation and calling out in people who are unable to verbally express their discomfort. Many people with later dementia have painful conditions associated with ageing, so this cause of BPSD needs to be actively considered and treated with adequate analgesia. People with later dementia are at increased risk of delirium as brain reserve diminishes. The characteristic sign is a sudden change in behaviour, often recognized by people who know them well. A physical examination and review of medication is necessary, and a delirium screen including blood tests and a urine sample may be required. If the patient requires admission to general hospital for appropriate treatment of physical causes, hospital staff should be advised that the change in environment is sufficient to worsen confusion (and BPSD) in people with dementia.

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Psychological causes of BPSD

Depressive symptoms are common in later dementia and may present with challenging behaviours such as agitation, anxiety, irritability, calling out, crying, and clinging to people for reassurance. Risk factors for depression in dementia are family history, past history, younger age at onset of dementia, and female gender. An unhappy childhood may be relevant, particularly as people with later dementia are often reliving their childhood memories by this stage in the disease and no longer have the psychological defence mechanisms to protect themselves against emotional pain. Depression in dementia may be precipitated by a change in environment, particularly the move into a care facility. The prevalence of depression among older people in long-term care is up to 35% (Thakur and Blazer, 2008) and in general hospitals is approximately 20% (Royal College of Psychiatrists, 2005), compared to a community prevalence of 5–10% (Copeland et al., 1999). Relationship factors such as bereavement or carer stress may also trigger depression, even if the person with dementia seems to be unaware of them. Affective symptoms in later dementia are similar to those seen in people without dementia and include low mood, social withdrawal, poor appetite and weight loss, disturbed sleep, tearfulness and depressive content to speech, and an expressed wish to either die or end their life. There may be diurnal variation of mood or other BPSD (e.g. calling out or aggression that is worse in the mornings but diminishes by the end of the day). The Cornell Scale for Depression in Dementia (Alexopoulos et al., 1988) is a useful rating scale to assess the severity of depressive disorder and to monitor its response to treatment, as it utilizes the observations of carers and staff.

Psychosis is also a common feature in later dementia and can present as agitation. As communication may be challenging, clinical observation is an essential component of the assessment, for example, signs such as plucking at bedclothes can suggest the presence of visual hallucinations. Psychotic symptoms could indicate a delirium or affective disorder, but may also be a characteristic of the underlying dementia of any aetiology, but most commonly LBD. Hallucinations may be perceived as a threat so may result in behaviour aimed at self-defence, including verbal and physical aggression towards others or barricading themselves away from others.

Environmental and social causes of BPSD

Assessment of all dementia, but particularly dementia in the later stages, requires an evaluation of the context or system in which the person with dementia is living; assessments of the living situation and significant relationships are paramount. This applies whether the person is living in the family home, is in residential care, or in the general hospital. People with later dementia are easily disorientated, confused, and frightened by new environments and unfamiliar people. Changes can precipitate behaviours that challenge, particularly if staff do not understand why

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patients are fearful and aggressive, shouting for help, or perhaps urinating inappropriately because they cannot find the toilet. Behaviours such as aggression, agitation, apathy, and shouting also increase the potential risk of abuse from some carers—either through neglect of the person (particularly if staff do not know how to manage the behaviour) or by more deliberate acts, such as physical aggression or restraint, psychological bullying, or sexual exploitation. Furthermore, abusive behaviour from carers can often be overlooked as a *cause* of BPSD.

Management of later dementia

The progressive nature of dementia means that there are additional management issues in later stages. This section focuses on i) the ongoing requirement for person-centred and relationship-centred care in later dementia, ii) management of BPSD, iii) making decisions for people who no longer have capacity to do so for themselves, and iv) end-of-life care for people with end-stage dementia.

Person-centred and relationship-centred care

Person-centred care remains at the heart of the management of later dementia, but it can be challenging to maintain this approach with individuals who are unable to articulate their opinions about choices in life. Hence, the central task in the management of later dementia is to facilitate communication and respect for the person's life-long preferences as far as possible in all areas of decision-making, while also providing care that is safe, lawful, and optimizes quality of life for people with dementia and their caregivers. The concept of 'personhood', i.e. respecting and valuing each person regardless of the extent of impairment, is especially important in the later stages of the disease, and is fundamental to maintaining positive social relationships in dementia (Kitwood and Bredin, 1992). As people get older, their family and friends may pass away and with them the biography, life stories, and experiences of the person with advanced dementia. Unless there is a proactive attempt to preserve the people's identity by creating sufficient documentation of their existence, people with dementia can be left with no life context, which makes it much easier for other people to treat them as 'nonpersons', and increases the potential risk of neglect and abuse. One of the ways in which this can be achieved is by life story work, which aims to capture memories in imaginative ways that may include words, photographs, and music, which can be stored in various formats, e.g. in a scrapbook or on a DVD (Moos and Bjorn, 2006). In the UK many health and social care organizations use the Alzheimer's Society *This is Me* booklet, in which family and professionals can record details of a person's cultural and family background; events, people, and places from their lives; preferences, routines, and their personality. This enables health and social care professionals to tailor care specifically to the individual. For instance, if a person has a lifelong habit of walking or gardening, then an attempt to get outside does not have to be wrongly interpreted as an attempt to leave. These tools help caregivers to know the person behind

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the dementia, and allows them to respect the person's preferences for food, music, hobbies, and people, as well as his/her spirituality and religion.

Management of BPSD

Because of the complex causes of BPSD, a 'one size fits all' management solution does not exist (Kales et al., 2015). Management includes both nonpharmacological and pharmacological approaches that have to be tailored to the person with dementia, their caregivers, and the environment. This has been described as the DICE approach—*Describe the problem, Investigate the cause, Create a plan, Evaluate its effectiveness* (Kales et al., 2015).

Nonpharmacological management of BPSD

Nonpharmacological approaches are the first-line management for BPSD; they include person-centred care, caregiver support, and improving social interactions (Department of Health, 2009; Alzheimer's Society, 2011). Pharmacological approaches should only be considered first-line when there are clear indications, such as significant risk of harm to self or others, as exemplified in Fig. 36.2. Non-pharmacological interventions are essentially good quality care so can also be seen as effective in preventing BPSD. Environmental factors that have been identified in the assessment must also be addressed. If the person with dementia is living in a care home, then familiar items such as furniture and photographs can help to maintain a sense of security, trust, and comfort in an increasingly disorientating and confusing world. Equally important is the presence of a calm and friendly routine with familiar carers. Relating to the person with dementia rather than to the patient with a disease is particularly important, and requires the provision of good quality educational programmes. Box 36.1 demonstrates how good communication skills are essential during everyday tasks such as personal care. Specific non-drug treatments for BPSD recommended in the NICE dementia guidelines include aromatherapy, animal-assisted therapy, massage, multisensory stimulation, therapeutic dance, and music therapy. Two recent systematic reviews (Livingston et al., 2014b; Kale et al., 2015) found that, whether delivered by family caregivers or care home staff, individually tailored interventions involving person-centred care and communication skills training had the most effective long-term effect in reducing agitation in later dementia.

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Fig. 36.2

Pharmacological approaches should only be considered first-line when there are clear indications, such as significant risk of harm to self or others.

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Box 36.1 Example of communication skills and person-centred care for agitation during personal care

Communication skills and person-centred care involve considering what the person with dementia understands, is trying to say, and what they want, rather than being focused on completing a task, such as personal care, to help them. It involves verbal and non-verbal communication.

This example is about being aware that someone with dementia who requires personal care might not understand or remember this. When that happens, well intentioned, necessary care might be experienced as assault and the person could become agitated. The principles of communication are to:

- Identify yourself and others if the patient does not remember
- Explain what is happening, when it is happening, one step at a time (because the person with dementia might not remember)
- Use calm, reassuring tones

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- Ensure you can be heard
- Avoid negative words and tone
- Ask one thing at a time
- Speak slowly
- Allow the person with dementia sufficient time to respond
- Offer simple choices (no more than two at a time)
- Help the patient find words for self-expression (and check if you have understood correctly)
- Lightly touch to reassure, calm, or redirect
- Use relaxing sensory stimuli, such as music or soft lighting, if they enjoy it

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Advanced dementia can have a devastating impact on family caregivers, who are often older and may be frail themselves. Without support, they frequently end up exhausted, isolated, and unable to cope. It is at this point that people with later dementia may present in crisis, when their carers can no longer look after them due to their own physical or psychological ill health. Specialist dementia care services can support carers by facilitating access to transport, sitting services, day care, domiciliary care, night sitting services, and respite care in the person's own home or in a care home, as well as provide psychosocial support for the carers themselves.

Pharmacological management of BPSD

Physical causes of BPSD should be considered and treated, for example, giving antibiotics for a respiratory or urinary tract infection. Pain is a common cause of BPSD and a recent trial reported that treating behavioural symptoms with a trial of stepped analgesia (most receiving paracetamol) significantly reduced agitation in people with moderate to severe dementia (Husebo et al., 2011).

If a depressive disorder is suspected, then treatment with antidepressants might be considered. There is little evidence that antidepressants are effective in depression in people with dementia (Farina, 2017) but studies are frequently statistically underpowered. A recent large UK study (Banerjee et al., 2011) that compared the effectiveness of sertraline and mirtazapine with placebo reported that the two antidepressants had no greater benefit and increased the risk of adverse events. However, all three treatment groups showed a consistent improvement in depression

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rating, indicating that non-drug treatments deployed by community mental health teams may be the most helpful intervention for depression in dementia. The most recent recommendations (Livingston et al., 2017) are that antidepressants should not be started in people with dementia, unless there is a history of depressive episodes before the dementia, or if the patient has not responded to social or psychological treatment and is moderately or severely depressed.

Antidepressants are sometimes used to treat agitation in later dementia (Farina et al., 2017). The SSRIs citalopram and sertraline, but *not* trazodone, are effective in reducing agitation, and the addition of a psychosocial intervention to citalopram was found to be more effective than the psychosocial intervention alone for both agitation and caregiver distress (Porsteinsson et al., 2014).

If BPSD continue to cause distress, or if there are significant risks to the person with dementia and/or others, then short-term treatment with other psychotropic medication may be considered. Antipsychotic drugs have the strongest evidence base (Kale et al., 2015) but, in recent years, there has been considerable concern about the risks associated with the use of antipsychotic drugs to control challenging behaviour. Antipsychotic medication has sometimes been used to treat the symptoms without addressing the cause of the behaviour: this is unacceptable and puts people with dementia at risk, as antipsychotics have been reported to increase the risk of cardiovascular events, extra-pyramidal side effects, and falls, as well as increasing mortality (Ballard and Waite, 2006; Banerjee, 2009). Thus, the only indication for the use of antipsychotic medication is where the patient is severely distressed and agitated and nonpharmacological methods have failed, and/or if the patient or others are at risk. Antipsychotics do not improve restlessness or non-aggressive behavioural symptoms in dementia but can reduce aggression and psychosis (Ballard and Waite, 2006). The two drugs with the best evidence of effectiveness are risperidone and aripiprazole, but other atypical antipsychotic drugs such as olanzapine and quetiapine are also used in practice. Current advice is that treatment should be targeted at specific symptoms, which should be precisely described at baseline and at frequent follow-up; and that treatment is reduced and discontinued within three months (Fig. 36.2; Banerjee, 2009; Alzheimer's Society, 2011). Antipsychotic medication should be avoided in LBD, as antipsychotics can cause acute dystonia and sudden death (McKeith et al., 1992). Cholinesterase inhibitors are usually used as a first-line treatment for psychosis in LBD, but if these are ineffective then the antipsychotic quetiapine may be tried as it appears to have the fewest side effects of the atypical antipsychotics and is sometimes effective (Zahodne and Fernandez, 2008). There is some evidence that the antipsychotic clozapine is useful in treating psychosis in Parkinson's disease dementia, but no studies have been carried out in LBD to date (Weintraub and Hurtig, 2007).

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Benzodiazepines are usually avoided in older people because they can increase confusion and the risk of falls. However, those with a shorter half-life, e.g. lorazepam, are sometimes used in the short-term treatment of agitation.

Cholinesterase inhibitors may be of benefit in non-cognitive symptoms, including depression, apathy, and anxiety, but not agitation or aggression (Howard et al., 2007). Rivastigmine and donepezil, and to a lesser extent galantamine, have all been shown to be effective in treating cognitive function and behavioural disturbances in LBD (Matusunaga et al., 2016). Post hoc analyses of trial data suggested that memantine may also be effective for the treatment of agitation in dementia but a trial designed to test this hypothesis (Fox et al., 2012) found that memantine did not improve agitation in mild to moderate Alzheimer's disease.

Anticonvulsants have been reported as effective in the treatment of aggression and agitation in some small trials. Carbamazepine has the best evidence (Yeh and Ouyang, 2012) but has a number of serious adverse side effects, so is usually avoided. Lonergan and Luxenberg (2009) reported in a Cochrane review that valproate was ineffective and was associated with an unacceptable rate of side effects.

Management of sexually inappropriate behaviour

Sexually inappropriate behaviours have been defined as 'sexual behaviours not suited for their context and which impair the care of the patient in a given environment' (Black et al., 2005). What constitutes appropriateness will depend on the participants' capacity to consent and the opinions and judgments of staff and relatives who are providing care. Sexually inappropriate behaviours, although present in only 7% of people with dementia (Burns et al., 1990), frequently cause concern, particularly in institutional settings. The behaviours include sexualized remarks, grabbing, exposing, public masturbation, fondling, sexual advances to staff or other residents, implied sexual acts (e.g. requesting unnecessary genital care), and attempts at genital contact or penetration. As with other BPSD, it is important to search for physical and psychological causes. Sexual contact may be a source of comfort in people with dementia who are anxious, depressed, or lonely. The choice of treatment depends on the urgency of the situation, the type of behaviours, and the underlying causes. Nonpharmacological approaches are used first-line, and include boundary setting: giving clear instructions for appropriate behaviour and provision of private rooms, as well as reducing the reinforcements of behaviour. Physical disorders, delirium, affective disorders, and psychosis can all trigger sexual behaviour, so should be assessed and treated. If the behaviour presents a risk to the person or others, then clinicians often resort to a variety of pharmacological agents, such as SSRIs, antipsychotics, or antiandrogens (De Giorgi, 2016).

Sexual behaviour between residents in care homes often causes concern. Some staff may feel that the behaviour is inappropriate, particularly if the person with dementia still has an involved partner, or that one or both

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residents are unable to consent to the behaviour. Others may feel it is every person's right to have a sexual relationship while ignoring potential vulnerability and risks. Health and social care professionals need to be able to establish the capacity of the people involved to consent to the sexual activity in the new relationship. If the person with dementia does not have capacity to consent, then a sensitive discussion with staff and family about the appropriateness of the relationship (taking best interests into account) is required. These matters are complex and raise emotive issues, so a frank discussion and subsequent shared agreement with all involved is a worthwhile exercise.

Risk assessment and risk management

Ongoing risk assessment and management is vital in later dementia, identifying the risks to the person with dementia and possibly also to others. If the person with dementia is living alone in his or her own home then self-neglect, wandering, fire risks, falls, and medicines management are the commonest risks to self. The person with dementia, and particularly with BPSD, may also be a risk to others. For example, there may be physical aggression towards a spouse who is no longer recognized and thought of as a stranger, or to a care home assistant who is trying to provide personal care. People with dementia may respond to hallucinations, delusions, or irritability associated with depression or pain, by making accusations or hitting out at those nearest to them. Those nearest could be family members or carers, but in a care home environment they might also include other residents, and even other residents' visitors, some of whom may strike back. Under these circumstances, in the UK, it is recommended to inform the appropriate local authorities regarding the safeguarding of the person with dementia and other vulnerable adults, and to ensure that appropriate action is taken to reduce the risks to the person with dementia and to other adults (Department of Health and Home Office, 2000; Association of Directors of Social Services, 2005). People with later dementia may also live with their families where young children are present. The risks to younger children should always be considered, including the risk of aggression and inappropriate sexual behaviour, but also the possible risk of neglect if children are left in the care of the person with dementia.

Some risks can be easily addressed, for example, arranging for medication to be supplied in a blister pack or dosette box, or setting up the delivery of 'meals on wheels'. Risks around aggression, psychosis, and suicidality can usually be managed by involving the community mental health team who will give support and advice to family members or carers to reduce the chance of harm to self or others. If the risk to themselves or others is substantial, then the person with dementia may require admission to an inpatient mental health unit for assessment and treatment. Other people with dementia do not require psychiatric admission but are no longer capable of taking care of themselves at home and require placement in institutional care. In the UK, the Mental Health Act (2007) can be used to require people (who are unable to give

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informed consent) to reside at a specified place in their best interests under a guardianship order. However, most people with dementia move into residential care without needing to employ these measures; the move is usually unproblematic if family and staff handle it sensitively. If the person with dementia expresses a wish to leave after the move has taken place, then, in the UK, the facility makes an application to the appropriate supervisory body for assessment under Deprivation of Liberty Safeguards (DoLs) to make a judgment as to whether the person who lacks capacity can be lawfully detained in the facility. These processes are necessary to protect the person with dementia but are both lengthy and cumbersome; the Law Commission has recommended streamlining the process with a new scheme called the Liberty Protection Safeguards (<http://researchbriefings.files.parliament.uk/documents/CBP-8095/CBP-8095.pdf>). This is discussed further in Chapter 58.

People with dementia are vulnerable to abuse and exploitation, and risk of abuse by others increases as the dementia progresses, as they become less able to protect themselves and less able to complain. A systematic review found that, globally, one in four vulnerable older people were at risk of abuse (Cooper et al., 2008), both in their own home and in institutional settings. The commonest forms of abuse of vulnerable adults are psychological, physical, neglect, sexual, financial, and discriminatory. Signs that might alert health and social care professionals to the possibility of abuse include fear or agitation in the presence of the abuser, bruising to the face and body, and the appearance of pressure ulcers. In the UK, the Mental Capacity Act (2005) has introduced significant new protections from abuse for people who lack capacity by creating the criminal offences of ill treatment or wilful neglect: these offences can be committed by anyone responsible for the person's care.

Making decisions for people who no longer have capacity

When people with dementia no longer have capacity to make decisions about their health, welfare, or financial matters and they have not made advance directives, then decisions have to be made in their best interests by proxy decision makers. Under the Mental Capacity Act (2005), health and social care professionals can work with families to come to decisions in the person's best interests. In the case of a person refusing pharmacological treatment, this may result in the decision to covertly administer medication to the person with dementia in order to improve his or her physical and/or psychological wellbeing. Best-interest decisions cannot be made for financial matters, so if advanced provision has not been made, then, in the UK, the family are advised to apply to the Court of Protection to ensure that they are legally protected to make financial decisions on behalf of the person with dementia.

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End-of-life care

The progressive nature of dementia means that a palliative care approach to management is employed throughout the course of the disease until death. This approach aims to optimize quality of life for people with dementia and their carers and to ensure that they are supported with both dignity and respect and treated as persons throughout. However, when a person with dementia is at the end of life, there are issues that are specific to dementia that need to be addressed. As people with end-stage dementia are unlikely to have capacity to make decisions about their healthcare, and have limited ability to communicate their needs, it will fall upon the carers of people with dementia to make choices in their best interests. This is best done using an individually tailored end of life care plans which aims to support both the person and the family in optimising quality of care at the end of life. A good plan includes timely decisions about place of care, nutrition, withdrawing or withholding treatment, and cardiopulmonary resuscitation. Advanced care planning allows the family to state clearly what their wishes are for their relative and to ensure that ethical and legal principles are upheld, thus safeguarding the person with dementia, themselves, and the healthcare team who are providing care. It can be difficult to recognize dying in end-stage dementia (compared to terminal cancer, for example) but it is an important skill, informing the family that death is imminent so that religious or spiritual needs can be met. Drugs used in end-of-life care are usually to manage symptoms such as terminal agitation and restlessness. Other drugs are usually discontinued, as long as this does not lead to distressing withdrawal effects. Respiratory tract secretions cause noisy breathing (the 'death rattle'), which may be upsetting for the family and carers; these can be managed by repositioning of the patient, suction if appropriate, and administration of hyoscine. The most important aspect of management is good communication with the family and primary care team to ensure people with dementia and their relatives experience a 'good death'.

Conclusion

The general management of dementia includes the understanding of not only complex medical problems, with interplay of physical and emotional wellbeing, but also complex social, ethical, and legal issues. Quality care cannot be achieved by families and unskilled workers alone. There is a need for education and support from skilled dementia specialists with broad-ranging knowledge and a willingness to educate others. Improved recognition of dementia will come about with improved public education about the disease. Better management of the disease will happen when society accepts the increasing likelihood that each and every individual will either suffer with dementia or know someone with dementia, and wants to improve the experience for all involved.

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Delirium

Chapter: Delirium

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Introduction

Delirium, described in medical texts since antiquity, is a neuropsychiatric disorder arising from an acute pathophysiological disturbance, which could include brain injury, physical disease or injury, drug treatment or drug withdrawal. Its core characterization is distinctively described as 'clouded consciousness', often operationalized as altered arousal and inattention, and associated with acute onset and fluctuating cognitive and perceptual changes. Most of the burden of delirium is in acute hospitals, but its prevalence is intimately related to high levels of frailty and prior cognitive impairment. Therefore, while it commonly presents to liaison psychiatry services, it also often presents in persons living with dementia in community settings, including care homes. Delirium is independently associated with poor outcomes, including increased mortality rates and incident dementia (Witlox et al., 2010, Davis et al., 2012).

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Despite the considerable patient and population impact, delirium is generally under-recognized, under-managed, and under-researched. This chapter discusses the definition of delirium and its operationalization in clinical and research contexts. We review some of the major theories underlying delirium pathophysiology, going on to discuss screening, prevention, and treatment, as well as delirium in specific situations, including care homes and in palliative care.

Definition

There are some differences in emphasis across the nosological classifications for delirium in the International Classification of Diseases (ICD) and Diagnostic and Statistical Manual (DSM), as well as historical evolution of the diagnostic criteria (Sepulveda et al., 2016), though all rely exclusively on clinical evaluation. In general, the DSM approach has been less restrictive than ICD, and the DSM-IV definition is the most widely used reference standard for research studies. This diagnostic drift makes comparisons for the purposes of psychiatric epidemiological studies more difficult, but there is a core constellation of symptoms that comprise the syndrome regardless of the classification system.

Essentially, four domains underlie the delirium construct. The first is that there must be a disturbance in consciousness, and this is operationalized to consider both *level* and *content* of consciousness (respectively, level of arousal and inattention). The second is that the disturbance is acute, usually evolving over hours and days, and that this tends to fluctuate. Thirdly, there must be changes in other cognitive, perceptual, or emotional/affective domains (e.g. memory impairment or psychotic features). Finally, it must be apparent that these changes are due to an underlying acute physiological disturbance, often medical, surgical, or anaesthetic. In general terms, delirium might be regarded as a decompensation of global cerebral function under the stress conditions of being unwell.

Each of these domains merits more detailed consideration, particularly because the boundaries of each criterion are not precisely defined (Davis et al., 2013). The notion of acute physiological disturbance is often straightforward but is important to note that there are often multiple contributing causes. In practice, management aims to identify and optimize as many physiological abnormalities as possible and assess the subsequent effect on delirium (see General principles of management). It is sometimes the case that the direct precipitant is difficult to uncover, or it may be inappropriate to investigate exhaustively (for example, in palliative care; see End-of-life delirium). Nonetheless, identifying and managing any physiological disturbance must take precedence (along with ensuring safety and relieving severe distress) in any differential diagnosis that includes delirium (including states such as behavioural and psychological symptoms of dementia or deterioration in Lewy body disease). In other words, it is safest to assume that crises or acute changes are due to delirium so as not to miss an underlying physical

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illness—at the same time being sensitive to the possibility that hospital admission and change in environment risks worsening delirium.

The requirement for additional domains in cognition to be disturbed reflects that delirium represents global brain dysfunction. Psychotic symptoms are not an essential criterion, though these may have most impact in terms of distress for patients and their families (Partridge et al., 2013). What is less clear is how much cognitive change needs to be demonstrated (or be certain of) in order to establish delirium onset. ‘Change’ is usually ascertained through taking the history (including collateral history from informants and/or care staff).

The time course and fluctuation of symptoms tends to be quite specific to delirium (though there are mimics). Usually, delirium onset evolves over hours and days, though whether it is possible for delirium to take several weeks to develop is not clear. In addition, the time course of delirium resolution is very variable. In some cases, delirium has been suggested to persist for several months or even years (Cole et al., 2009).

The aspect of delirium essential to appreciate is the ‘clouding of consciousness’. The specific term ‘clouding of consciousness’ was separated out into ‘awareness, attention, and arousal’ in DSM-5 to enable more a precise operationalization. However, it remains a useful concept particularly because it distinguishes delirium from dementia, at least in the latter’s mild-to-moderate stages. We emphasize that ‘altered consciousness’ represents a fundamentally dysfunctional physiological state (although, of course, attention may be poor when tired, sleep deprived, anxious, stressed, pre-occupied, or intoxicated). Being in clear consciousness—able to divide and focus attention—is a highly evolved, high-order function. Therefore, when this is disturbed for any reason, it is highly adverse. This is usually readily appreciated when head injury leads to abnormal consciousness, yet exactly the same state caused by dehydration or a respiratory tract infection does not always attract the same degree of clinical urgency. *Consciousness* is a distributed neurological function: there are bottom-up aspects arising from the reticular activating system (associated with arousal), and there are top-down aspects relating to the frontoparietal cortex that enable focused and sustained attention. These two aspects therefore relate to both *level* and *content* of consciousness respectively, and these are hierarchically related (European Delirium and American Delirium, 2014). In practice, this means that *content* of consciousness (attention) can only be assessed if *level* of consciousness (arousal) is sufficient. Detailed cognitive testing focused on establishing attentional deficits may not even be possible if altered arousal precludes testing. The corollary is that altered arousal (short of coma) itself should be considered to be a severe presentation of inattention and therefore could be delirium.

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Delirium subtypes

One of the most striking aspects of delirium presentations is the marked differences that may occur in motor-arousal subtypes. Hyperactive delirium—hyperarousal and psychomotor agitation—is the more easily recognized presentation. Hypoactive delirium is associated with reduced arousal and psychomotor retardation and is more likely to be missed as a diagnosis. It is possible that this lower recognition rate is associated with higher mortality because of unrecognized acute illness (Jackson et al., 2016b), though equally, it may reflect a predominantly brainstem (rather than cortical) disturbance. Overall, hyperactive presentations are less common than hypoactive ones (20% versus 80%; Kiely et al., 2007). However, over time, most delirium is mixed and will tend to fluctuate between the two states.

Delirium superimposed on dementia

Delirium is intimately associated with dementia. Dementia is the principal risk factor for delirium, and delirium reciprocally worsens dementia. Among hospital presentations with delirium, the majority of patients will have underlying dementia whether or not that dementia has been diagnosed (Jackson et al., 2016a). As such, people with delirium represent a pool highly likely to have dementia, with implications for future engagement with memory services. In addition, there is now emerging understanding the delirium itself is prospectively associated with worsening cognition and incident dementia (see Long-term cognitive outcomes).

Diagnosing delirium in patients with dementia is challenging. There is no definite reference standard which accounts for their co-presentation (Morandi et al., 2017). Indeed, DSM and ICD conceptualize the syndromes as being mutually exclusive ('deficits not otherwise attributable to delirium/neurocognitive disorder', respectively). Nonetheless, a presentation with abnormal arousal and attention usually indicates superimposed delirium, as arousal is often normal unless dementia is advanced, but even this can be difficult to detect. Probably the commonest presentation is of abrupt change in cognition or behaviour causing a crisis ('more confused'; 'newly agitated or aggressive'), and these cases should be assumed to represent delirium until proven otherwise.

Delirium epidemiology

The epidemiology of delirium has not been as comprehensively studied as other acute conditions of ageing such as stroke or cardiovascular disease. Community studies suggest that point prevalence of delirium is around 1% in older people, in essence highly associated with dementia prevalence (Davis et al., 2013). As such it is more common in older age groups and in care homes. Hospital studies of delirium are more common and suggest that 15 to 20% of the adult inpatient population has delirium at any one time, though this will be higher in acute medical admissions

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(30%), patients with hip fracture (15% at admission, 50% at any time), and in intensive and palliative care (50% or more) (Vasilevskis et al., 2012).

Pathophysiology

The heterogeneous aetiology, clinical presentation, and course of delirium suggest that it cannot be due to a single underlying neuropathological process. Whether 'delirium' is a label for an array of neuropsychiatric syndromes with similar clinical features but diverse underlying neurochemical disturbances, or whether there is a final common neurochemical pathway is yet to be determined. A number of plausible and complementary theories for the development of delirium have been postulated. It is likely that delirium pathogenesis is a complex hybrid of these, resulting from multiple disturbances in neurochemical signalling in the context of an acute insult to the brain.

There is an inverse relationship between the number or severity of predisposing and precipitating factors required to produce delirium (Inouye and Charpentier, 1996; Quinlan et al., 2011). In young healthy adults, the severity of acute insults needed to precipitate delirium is high, for example, meningitis or adult respiratory distress syndrome (as suggested by the high occurrence of delirium in patients treated in intensive care units (Salluh et al., 2010; Roberts et al., 2005; Cavallazzi et al., 2012)). However, in those who are older, frailer, or have pre-existing cognitive impairment, relatively trivial precipitating factors may be sufficient, for example, mild hyponatraemia, or a viral infection. At this end of the spectrum, frailty and pre-existing dementia are probably 'more important' than the precipitating factors and so particular concern should be raised when delirium is demonstrably due to minor physiological disturbance because this de facto indicates frailty (Dani et al., 2017; Eeles et al., 2012). Delirium can be provoked in those with previously healthy brains if the physiological insult is large enough. These observations suggest that likelihood of development of delirium is a continuous function of the underlying vulnerability and the size of the insult (see Fig. 37.1). A better understanding of the neuropathological processes that contribute to delirium is key to identifying biomarkers and potential drug targets. Key theories of delirium pathogenesis are outlined here; these have been reviewed in more depth elsewhere (Maldonado, 2008, 2013, 2018).

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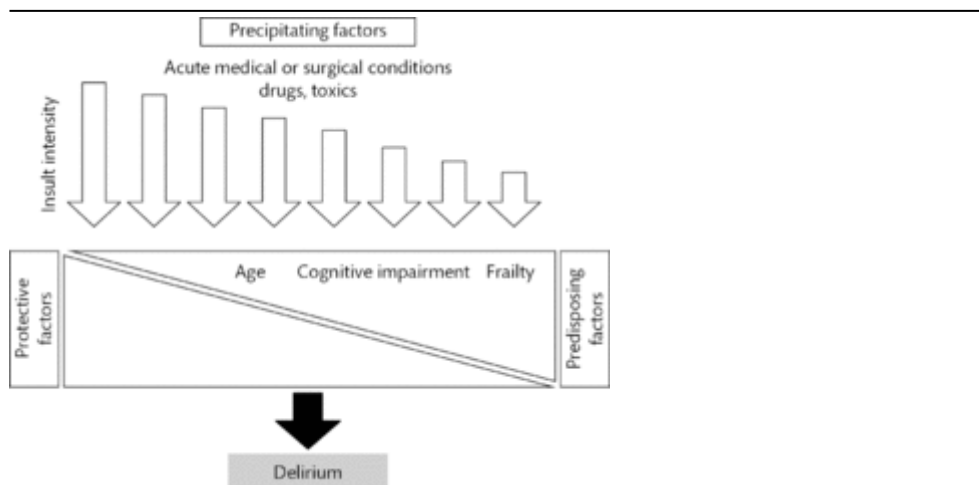


Fig. 37.1

Relationship between predisposing, protective, and precipitating factors in delirium.

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Direct toxic brain insults

Direct toxic insults to the brain (e.g. drugs, hypoxia, sepsis, metabolic disturbance, acute brain injury, or stroke) can disrupt brain functioning through dysregulation of normal neurotransmitter signalling and energy metabolism. If these insults are of significant magnitude, delirium may result even in those with previously 'normal' brains.

Neurotransmitter hypothesis

An imbalance in neurotransmitters has been postulated as being central to the development and clinical manifestations of delirium. Reduced acetylcholine, elevated catecholamines (dopamine and noradrenaline), and elevated glutamate and its derivative gamma-aminobutyric acid (GABA) may be implicated (Maldonado, 2013). The exact pattern of these disturbances may underlie arousal-motor subtypes, with relatively higher noradrenergic drive responsible for hyperactive presentations and hypocholinergic states linked to hypoactive delirium.

Acetylcholine is involved in attention and awareness and reduced acetylcholine has been identified as a potential 'common denominator' in development of delirium (Hsieh et al., 2008). Drugs that antagonize acetylcholine are potently deliriogenic, but the picture is not clear as

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attempts to prevent or treat delirium through increasing acetylcholine with cholinesterase inhibitors (e.g. donepezil) or pro-cholinergic drugs have been disappointing (see Pharmacological prevention). This could indicate that reduced acetylcholine frequently coexists or is a result of delirium, rather than being directly implicated in development of delirium (Schor et al., 1992; Marcantonio et al., 1994)

Elevated levels of the monoamines dopamine and noradrenaline have been associated with delirium. It has been suggested that dopamine is particularly implicated in development of psychotic features, a theory supported by the use of antipsychotic medications (haloperidol, olanzapine) to control these (van der Mast, 1998). Conversion of dopamine to noradrenaline is oxygen dependent, and degradation of excess dopamine cannot occur in the presence of toxic metabolites at times of cellular hypoxia (Maldonado, 2013). Dopamine potentiates the excitatory neurotransmitter glutamate and its calcium-mediated neurotoxic and deliriogenic effects through direct action on voltage-gated NMDA receptors (Maldonado, 2013; van der Mast, 1998). The inhibitory neurotransmitter GABA is a derivative of glutamate. These, the most prevalent neurotransmitters in the brain are closely involved with oxygen-dependent glucose metabolism and particularly susceptible to disruption at times of hypoxia (van der Mast, 1998). Drugs with GABA-ergic properties (e.g. benzodiazepines) have been shown to be particularly deliriogenic (Pandharipande et al., 2007).

Other neurotransmitters implicated in delirium include serotonin (5-HT) and histamine, either of which may be elevated or reduced during episodes of delirium.

Neuroinflammatory and exaggerated sickness behaviour hypothesis

Systemic inflammatory stimuli are relayed to the brain via neural and humoral pathways (e.g. via the vagus nerve, or circulating cytokines). In response to these stimuli, the blood-brain barrier may be compromised, resulting in neurochemical disturbance that presents as a 'sickness behaviour' response: withdrawal, malaise, lethargy, and, in those who are susceptible, delirium (Cunningham and MacLulich, 2013).

Microglia are the brain's macrophages. In a healthy brain, they migrate to areas of potential damage (e.g. during hypoxia), become activated, and mediate a coordinated neuroprotective inflammatory cascade (including release of cytokines) to phagocytose dead or dying neurones (Neumann et al., 2009). There is evidence from animal models that, in brains with neurodegeneration, microglia exist in a 'primed' pro-inflammatory state (Perry et al., 2010). This pro-inflammatory state causes microglia to over-respond to stimuli that would otherwise be well controlled in a brain without pathology—the activation response becomes dysregulated, exaggerated, and neurotoxic (Murray et al., 2012). Primed microglia are thought to play a role in neurodegenerative diseases such as Alzheimer's dementia, which may help to explain the propensity to delirium resulting

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from minimal insults in patients who have underlying neurodegenerative disease.

Oxidative stress hypothesis

Relative tissue hypoxia resulting from increased oxygen demand and cerebral hypoperfusion at times of acute illness may lead to accumulation of reactive oxygen species (ROS) (Maldonado, 2013). In the absence of sufficient antioxidant (e.g. at times of physiological stress) this results in redox imbalance, oxidative stress, failure of ATPase pumps, and destabilization of the cell membrane (Garbarino et al., 2015). A critical threshold of cerebral hypoperfusion has been suggested, below which a cascade of events results in inactivation of calcium ATPase pumps, excess intracellular calcium, and neurotransmitter failure (Aliev et al., 2003). This includes release of the excitatory monoamine neurotransmitters (dopamine, noradrenaline), which act on NMDA receptors and potentiate glutamate-mediated neuronal damage. Excess flux of calcium into the intracellular space may therefore be a key contributor to delirium (Maldonado, 2018).

Neuroendocrine hypothesis (hypothalamic-pituitary-adrenal (HPA) axis)

Excess circulating cortisol has been associated with delirium (Mu et al., 2010). The mechanisms are not well understood, although a direct effect on function of the hippocampus (Maldonado, 2013) or augmentation of pro-inflammatory and ischaemic damage may be implicated (Sorrells et al., 2009). The limbic system is central to the regulation of HPA function (Jankord and Herman, 2008), and it is vulnerable to early pathology in Alzheimer's disease. Frailty has been associated with dysregulation of the HPA axis, resulting in chronically elevated levels of cortisol and disrupted diurnal cortisol variation (Varadhan et al., 2008). It is plausible that this chronic elevation in circulating cortisol may result in a reduced threshold for delirium in those with dementia or frailty—thereby responding at times of metabolic stress (e.g. infection), which results in further increases in cortisol (Maldonado, 2013). This is evident in patients with neurodegenerative conditions who show prolonged elevation of cortisol after the acute response (Otte et al., 2005; Magri et al., 2006). Similarly, patients with delirium have been found to have elevated serum and CSF cortisol in the context of sepsis (Pfister et al., 2008), hip fractures (Pearson et al., 2010), and cardiac surgery (Plaschke et al., 2010).

Melatonin dysregulation hypothesis

Disrupted sleep patterns have been implicated in development of delirium (Figueroa-Ramos et al., 2009; Watson et al., 2012); and this is thought to be mediated through melatonin. Melatonin resets the circadian rhythm and regulates the sleep-wake cycle. It is a ROS scavenger, an antioxidant, and has anti-inflammatory action (Maldonado, 2013). Despite this, therapeutic trials of melatonin for delirium prevention have not

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demonstrated any significant benefit (see section Pharmacological prevention)

Delirium prevention and multicomponent interventions

Nonpharmacological prevention

Nonpharmacological multicomponent interventions are the mainstay of delirium prevention in hospitalized older people. These interventions comprise two or more components delivered to patients or staff with the aim of reducing incident delirium, through addressing modifiable risk factors (see Causes of delirium). There is convincing evidence supporting this approach with a clinically important treatment effect across several randomized controlled trials in medical and surgical settings. Meta-analysis of trials of multicomponent delirium prevention interventions has demonstrated a risk ratio of 0.69 (95% confidence interval 0.59–0.85, seven studies of moderate quality, 1950 participants for intervention vs control; Siddiqi et al., 2016). Widespread adoption of multicomponent interventions for the prevention of delirium in hospitalized older people was recommended in the 2010 National Institute for Health and Care Excellence (NICE) delirium prevention guidance (Young et al., 2010). However, despite the consistent treatment effect seen in these trials, the content (number and nature of components) of these interventions are not standardized, and an optimal implementation strategy is yet to be specified.

Multicomponent intervention content

In the seven randomized controlled trials, the number of components varied between two and 13 (Siddiqi et al., 2016). Most included early mobilization (6/7) and reorientation strategies (5/7). Attention to sensory deprivation, nutrition, and hydration and an individualized approach to care each featured in 4/7 trials. Sleep hygiene (recognizing and respecting circadian sleep patterns), bladder and bowel care, and pain control featured in 3/7 of the interventions, while families bringing in familiar objects, active identification of infection, medication review, and attention to physiological parameters (oxygenation and electrolytes) were also reported.

Multicomponent intervention delivery

Methods of delivering multicomponent interventions varied considerably between trials. Most advocated an individualized approach to care (4/7) and this may be key to the success of these interventions. Checklists and protocols were used in 3/7 trials, while only one trial adopted multidisciplinary team (MDT) care (Lundstrom et al., 2007). Despite this, implementation of multicomponent interventions through the MDT is the approach advocated by NICE in the 2010 guidance (Young et al., 2010). Staff education and training appears to be integral to the delivery of

multicomponent interventions for delirium prevention; 4/7 trials included this as an explicit component of the intervention.

In addition to these trials, there have been several non-randomized studies of multicomponent delirium prevention interventions performed in different countries and across patient groups. These studies have produced a more pronounced treatment effect when compared to randomized trials of other multicomponent interventions (effect sizes between 0.44 and 0.59) (Vidan et al., 2009; Chen et al., 2017); the reasons for the apparently exaggerated treatment effects in non-randomized studies are likely to be methodological.

The most familiar nonpharmacological multicomponent delirium prevention intervention is the Hospital Elder Life Program (HELP) (Chen et al., 2015). This intervention comprises protocols aimed at improving orientation, reducing sedative use for sleep, early mobilization, correction of vision and hearing, and improving hydration for prevention of delirium in hospitalized older people. In the original (non-randomized) study, a before and after change in risk factors between control and intervention groups was achieved in only two of these six protocols (reducing sedative use, and improving orientation; Inouye et al., 1999). Despite this, the odds of delirium in intervention vs control groups was 0.60 (95% confidence interval 0.39–0.92). It is thought that part of the consistency in effect seen with the HELP intervention is the rigid training and fidelity to the protocols that is required for implementation. Whether or not this effect is generalizable to a population of older people in hospital outside clinical trials is unclear, and there have been significant implementation challenges in routine adoption of multicomponent interventions in non-research settings (Godfrey et al., 2013).

Despite the efficacy of multicomponent interventions in reducing incident delirium, there is no corresponding reduction in the more distal outcomes of mortality and admission to long-term care—despite the well-recognized relationship between delirium and these adverse outcomes (Teale and Young, 2015). The causes for this disconnect are unclear, but may relate to different aetiopathological mechanisms. For example, older people with frailty are particularly susceptible to delirium (Fig. 37.1) and its adverse outcomes (mortality, care home admission); in a frail subgroup of patients, non-modifiable risk factors (e.g. dementia) may be more prominent, and prevention of long-term adverse events much harder to achieve.

Further work is required to determine the optimal multicomponent intervention (i.e. identification of a parsimonious set of ‘active ingredients’), and the best system of care within which these should be embedded, including consideration of the environment, personalized care, implementation strategies, training, and education (for patients, their carers, and staff).

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Pharmacological prevention

Trials of pharmacological agents have been undertaken based on putative theories of underlying delirium pathophysiology. Several trials have investigated the acetylcholinesterase inhibitors routinely used for enhancing cognition in Alzheimer's dementia. Acetylcholinesterase inhibitors increase the available synaptic and post-synaptic acetylcholine and this offers a biologically plausible rationale for delirium prevention based on the association between delirium and acetylcholine deficiency (see Pathophysiology). A Cochrane review meta-analysis of trials of acetylcholinesterase inhibitors for prevention of delirium in hospitalized non-intensive care patients was limited due to the paucity of data available (Siddiqi et al., 2016). Overall, no benefit was demonstrated (relative risk 0.66 (95% confidence intervals 0.17-2.62), two trials, 113 participants; overall quality of evidence was low). A subsequent trial of rivastigmine for delirium prevention in patients in intensive care was stopped early due to excess mortality in the treatment arm (van Eijk et al., 2010).

Other drugs investigated for delirium prevention include the typical and atypical antipsychotic drugs (for their role in dopamine metabolism), melatonin (as a regulator of the sleep-wake cycle), and citicoline (as a cell membrane stabilizer through action on removing oxygen free radicals). Results have been disappointing, with none of these drugs showing significant benefit in terms of reducing incident delirium (Siddiqi et al., 2016). More recently, the intravenous sedative agent dexmedetomidine (an alpha-2 agonist acting on the locus coeruleus, inhibiting release of noradrenaline) has been trialled in intensive care settings with good effect in reducing incident delirium in critically ill older surgical patients vs placebo (OR 0.35, (95% CI 0.22-0.54); Su et al., 2016). Patients in both arms of this trial received other potentially deliriogenic drugs during the course of the trial but this was largely balanced between groups: benzodiazepines were used intra-operatively if required and this was less frequent in the intervention group (173/350 control vs 153/350 intervention). Similarly, both arms had patient controlled opiate analgesia post-operatively if needed (316/350 control vs 311/350 intervention). Although the aetiology and pathogenesis of delirium are likely to be different in the ICU setting compared with frail older people in medical and surgical inpatient settings, the apparent efficacy of dexmedetomidine to reduce incident delirium offers useful insight into potential mechanistic pathways.

Screening and diagnosis

Diagnosis of delirium is based on identification of the core features outlined in the DSM-5 criteria (American Psychiatric Association, 2013). Usually, this involves a bedside assessment supported by collateral information from relatives, carers, and ward staff. Primarily, the diagnosis of delirium requires a history of sudden onset of change in cognition (over hours or days) in any domain, with evidence of fluctuation usually over

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minutes or hours. Acute onset and the presence of fluctuation over the course of a day can help to distinguish delirium from other psychiatric syndromes, e.g. depression or dementia. Inattention (distractibility, poor concentration, and difficulty switching between tasks) has been identified as a key feature of delirium, but can be difficult to detect in the presence of dementia and depression. There are few clinical signs and symptoms specific to delirium, although visual hallucinations in the context of other features are suggestive (see behavioural and psychological symptoms). The presence of carphology (picking at bedclothes) and floccillation (picking at the air in front of the face) are closely associated with the presence of underlying delirium if they are seen, although their absence does not exclude it (Holt et al., 2015)

During more lucid periods, people with delirium may self-report feeling muddled, having difficulty with concentration, or experiencing (usually visual) hallucinations, but are they unlikely to offer this information spontaneously. It is therefore important to ask patients explicitly if they have experienced hallucinations, and to probe for evidence of delusions. It may be evident that patients are hallucinating during assessment, especially if they are looking at the floor or ceiling or pointing into space. Those with delirium may experience persecutory delusions, for example, that they are part of a conspiracy or that staff are trying to harm them.

There are a number of tools available to assist in the detection of delirium: simpler methods are used for delirium screening, while diagnosis of delirium involves training and lengthier assessments. Often patients are too unwell to undergo formal cognitive testing for delirium and a presumptive diagnosis is made based on available evidence. More in-depth delirium assessments are often reserved for reference-standard delirium diagnosis in research trials where criterion-defined delirium is a requirement to ensure precision. However, in clinical practice, a more pragmatic approach may be adopted if formal diagnostic testing is not feasible. Here, we outline some of the common approaches and established screening tests.

Screening tools

SQiD

The Single Question in Delirium (SQiD—‘Do you feel *your relative* has been more confused lately’) is a simple screen for delirium which has been suggested as a method to identify delirium for the purposes of the UK NHS standard contract (Sands et al., 2010). When asked of an informant that knows the patient well, the SQiD offers 80% (95% CI 28–99%) sensitivity and 71% (95% CI: 42–92%) specificity for the detection of delirium when compared with the Confusion Assessment Method (Sands et al., 2010). These data were taken from a small study (21 patients) in a palliative care setting, so there is doubt regarding generalizability. However, the SQiD is a useful and pragmatic first-line

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question which serves as an *aide memoire* to prompt a dialogue with relatives regarding recent changes in cognition.

Tests for arousal

Delirium results in deficits in the level or content of consciousness. In order to test the content of consciousness (e.g. attention), it is first necessary to determine the level of consciousness (arousal) to complete the tests. This may be performed at the bedside through informal assessment (can you rouse them sufficiently to engage in assessment?). If patients with suspected delirium are too drowsy or attention is untestable, assume delirium is present until proven otherwise. This inclusive approach is advocated by the European Delirium Association, and the American Delirium Society in a joint statement published in response to the updated DSM-5 criteria and to minimize the likelihood of missed opportunity to detect and manage delirium (European Delirium and American Delirium, 2014). Arousal can be assessed using tools such as the Glasgow Coma Score or AVPU system ('alert, voice, pain, unresponsive'), or more formally using methods such as the Richmond Agitation Sedation Scale or the Observational Scale for Level of Arousal (Chester et al., 2012; Tieges et al., 2013)

Tests for attention

Testing attention at the bedside can be done through observation during conversation and assessment. Patients with delirium are easily distracted by sights, sounds, and even their own thoughts and may flit between topics during conversation. Attention may be assessed more formally using tests such as the Months of the Year Backwards (MOTYB) test where patients are required to recite the months of the year backwards from December (O'Regan et al., 2014). They may self-correct, but do not offer prompts. Inability to reach 'July' without error implies inattention (83% sensitivity, 91% specificity), although accuracy is reduced in the presence of comorbid dementia. (O'Regan et al., 2014). Other tests such as serial sevens, digit-span tests, or counting backwards may be useful depending on intellectual and cognitive functioning.

The 4AT

The 4AT is a validated, simple, and attractive delirium and cognitive impairment screening test that is undergoing further comprehensive validation in a large multicentre trial (Shenkin et al., 2018). The approach combines four simple bedside tests of delirium features to give the likelihood that an individual has delirium (Table 37.1).

Delirium

Table 37.1 The 4AT, Version 1.2

				Score
<i>Alertness</i>	Normal (0)	Mildly sleepy (0)	Clearly abnormal (4)	0–4
<i>AMT4</i>	No mistakes (0)	1 mistake (1)	2 or more mistakes / untestable (2)	0–2
<i>Attention (MOTYB)</i>	≥7 (0)	<7 or refuses to start (1)	Unable / untestable (2)	0–2
<i>Acute onset or fluctuating course</i>	No (0)	Yes (4)		0–4
<i>Total score</i>				0–12

Score for each component in parentheses

≥ 4 possible delirium +/- cognitive impairment, 1–3 = possible cognitive impairment, 0 = delirium or severe cognitive impairment unlikely (but delirium still possible if [4] information incomplete)

MOTYB—Months of the Year Backwards

See <http://www.the4AT.com> for download and further information. Reproduced with permission from Alasdair MacLulich.

Delirium

Delirium Observation Screening Scale

The Delirium Observation Screening (DOS) scale is a 13-item tool (Schuermans et al., 2003). It does not require formal cognitive testing, rather being based on objective assessment of behaviours exhibited by patients and observed by nursing staff over the course of their shift (recorded three times a day) and is therefore useful for detecting fluctuations. The DOS is well-validated, well-completed, and has been used in different settings internationally. It takes under three minutes to complete and, due to repeated measurements, is an attractive approach to detecting newly-evolving delirium.

Confusion Assessment Method (CAM)

The Confusion Assessment Method (CAM) is often used for delirium diagnosis both in clinical practice and research (Inouye et al., 1990). It takes around ten minutes to complete, and requires a brief test of cognitive function and consultation with informants. The CAM operationalized DSM-III criteria and has been extensively validated. Rigid adherence to the CAM scoring system according to the coding guide is required. In addition, administration of the CAM requires formal training (including observed administration of the instrument and tests of inter-rater reliability) in keeping with the CAM training manual and coding guide, which limits utility by non-specialists in general clinical settings (Inouye, 2014). A number of variations in the CAM have been developed and validated for use in different healthcare settings—for example the CAM-ICU for use in critical care settings, a short-form of the instrument (3D-CAM), which can be completed in a few minutes and which embeds structured cognitive testing (Marcantonio et al., 2014), and the CAM-S, which can be used to grade delirium severity (Inouye et al., 2014).

Diagnostic tools for delirium

Gold standard delirium diagnosis involves expert assessment to elicit features of delirium in keeping with DSM-5 criteria. Some assessment instruments such as the Memorial Delirium Assessment Scale (Breitbart et al., 1997) and the Delirium-Rating-Scale-Revised-98 (DRS-R-98) (Trzepacz et al., 2001) are considered to be diagnostic rather than screening tools. These are typically lengthy to complete, precluding their use in routine clinical practice and are usually reserved for research use.

Causes of delirium, and the search for a cause

The simplest approach to managing delirium is to ‘identify the cause and treat it’. If delirium is a secondary response to physical illness, injury, or drug treatment, identifying the cause is fundamental. To do this successfully requires a thorough and systematic approach, knowledge of which potential causes to seek, and with what priority (i.e. look for the common or serious causes first).

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However, the simple approach raises questions and contradictions:

- A model of causation by a single diagnosis is inadequate; the model of predisposition and precipitant requires consideration of both
- In many cases, probably over half, multiple potential causes are present (Laurila et al., 2008; George et al., 1997). All require diagnosis and treatment, but their relative importance will usually be unknown
- Although diagnostic criteria specify that a general medical cause be identified in order to make a diagnosis of delirium, in many cases (15–20%) where delirium (or probable delirium) is diagnosed clinically, a sufficient or credible underlying cause cannot be identified despite investigation (Harwood and Teale, 2017)
- Diagnosis can be difficult in the face of severe illness, agitation, multi-morbidity, disability, and frailty
- It is easy to be diagnostically lazy, and attribute changes in mental state to infections (especially urinary) with insufficient supporting evidence
- In very frail or dying people, clinical judgment is required on a proportionate and humane approach to investigation, and associated investigation or treatment burden
- Distinguishing delirium, delirium complicating dementia, and decompensation of dementia can be difficult (Fong et al., 2015). A combination of physical and mental symptoms, and interpersonal, social, or environmental aggravating factors is likely to contribute to the clinical presentation or ‘phenotype’. The term ‘formulation’ may be more helpful than ‘diagnosis’.

A diagnosis is an explanation, in biomedical terms, of a set of signs, symptoms, or other findings (such as imaging). In most, but not all, cases it implies a pathological process. Among older people with multiple comorbidities this can be more difficult, and requires experience and thoroughness. Delirium is one of several presentations of illness with functional consequences or ‘geriatric syndromes’ (alongside falls, immobility, incontinence, ‘not coping’). The approach to all of these is similar: identify what has changed, treat the treatable, palliate symptoms and distress, make explicit efforts to restore or maintain function, and try to prevent complications and other adverse outcomes. Almost any medical or surgical diagnosis, drug, or trauma can cause delirium (or any other geriatric syndrome; Table 37.2).

Table 37.2 Causes of delirium.

Group	Examples

Delirium

<i>Brain diseases</i>	Meningitis, encephalitis, infarction, haemorrhage, tumours, trauma, post-ictal, non-convulsive status epilepticus
<i>Infections</i>	Neurological or systemic; consider skin, intra-abdominal/biliary, bone/joint/discitis, endocarditis, liver abscess, chest, urinary
<i>Drugs</i>	Opiates, anticholinergics, dopamine agonists, anti-epileptic drugs, high dose steroids. Intoxication or overdose.
<i>Drug withdrawal</i>	Alcohol, opiates, benzodiazepines
<i>Hypoxic</i>	Lung disease, heart failure, hypoventilation
<i>Metabolic</i>	Hyponatraemia, hypoglycaemia, hyper or hypocalcaemia, uraemia, hepatic encephalopathy
<i>Acute severe illness</i>	Myocardial infarction, acute urinary retention
<i>Post-operative</i>	
<i>Intensive care</i>	
<i>Trauma</i>	Hip fracture, head injury
<i>End-of-life</i>	
<i>Rarer causes</i>	Wernicke's encephalopathy, neuroleptic malignant syndrome, inflammatory/autoimmune encephalitis, limbic encephalitis

The usual approach to diagnosis can be followed: history, observation and examination, laboratory tests, imaging, and evolution over time—but adaptations are required. Some people with delirium may be too ill to give any meaningful information, while others are able reliably to report (current) symptoms. Collateral information from family, other informal or professional carers, or care home staff is mandatory, both for making the diagnosis of delirium, and determining its underlying causes. Previous medical history, time-course and nature of decline, and manifest symptoms may be reported.

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Examination may be conventional, or may have to be opportunistic and reliant on observation if the person is agitated or uncooperative. At minimum, try to describe the mental state, and examine for level of alertness, temperature and vital signs, oxygenation, neck stiffness, observable neurological function (communication, eye movements, facial palsy, limb tone, and movements), abdominal tenderness or rigidity, shoulder, hip and knee movement (for fracture or infection), skin (including under bandages), and evidence of pain or distress during personal care, rolling in bed, or transfer from bed.

Blood tests should include full blood count, electrolytes including calcium, inflammatory markers such as C-reactive protein, renal, and liver function (plasma ammonia if hepatic encephalopathy is suspected). Dipstick urinalysis is only useful if negative (thereby excluding UTI); otherwise microscopy and culture is required. Chest X-ray is more sensitive than clinical examination, and should be routine. Blood, sputum, CSF, or other fluid culture should be done if there is suspicion of infection. Further examination and investigation are directed according to initial findings or possible causes (Table 37.3).

Table 37.3 Possible additional (or 'second line') investigations.

Test	Looking for
Lumbar puncture, CSF examination	Evidence of infection (bacterial, tuberculosis, viral), protein, cytology
Electro-encephalogram	Epilepsy, non-convulsive status epilepticus, Creutzfeldt-Jakob disease
Autoantibodies (e.g. ANA, ds-DNA, ANCA, anti-TPO, VGKC, VGCC, NMDA, anti-neuronal)	Vasculitis, inflammatory encephalopathy
CT Chest abdomen pelvis (+/- Positron Emission Tomography)	Occult malignancy, infection including biliary or abscess
MRI spine	Discitis, osteomyelitis, tumour
Echocardiography	Endocarditis
Heavy metals, Insecticides	Poisoning
CSF, cerebrospinal fluid; ANA, anti-nuclear antibodies; ds-DNA, double stranded deoxyribose nucleic acid; ANCA, anti-neutrophil cytoplasmic antibodies; anti-TPO, anti-thyroid peroxidase; VGKC, voltage gated	

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potassium channel; VGCC, voltage-gated calcium channel; NMDA, N-methyl-D-aspartate

Neuroimaging (CT or MRI brain) is often performed, and is not unreasonable given the high stakes, but diagnostic yield is low (Lai and Wong Tin Niam, 2012). This will usually be required in the work up of possible coexisting dementia, or prior to lumbar puncture. It is mandatory if there is headache, persistent drowsiness, or focal neurological findings.

Prescribed drugs, and those bought 'over-the-counter' in pharmacies off-prescription, must be carefully reviewed. Some drugs are well-known culprits, including those with anticholinergic effects. Many other drugs have low-level anticholinergic effects, which, in combination in the context of polypharmacy, can add up. As a general principle of good medicines management, all drug prescriptions should be reviewed critically and regularly. Several anticholinergic burden scales have been developed (Salahuddin et al., 2015), which can be used as an *aide memoire*, to quantify risk from drugs, and as a justification for stopping them (which can be controversial with medical colleagues and families). These scales are all slightly different, and have been derived from historical datasets, so may not include all currently used pharmaceuticals. Table 37.4 includes an example.

Table 37.4 An anticholinergic burden scale.

Group 1 (low)	Group 2 (moderate)	Group 3 (high)
Ampicillin	Alverine	Atropine, hyoscine
Atenolol, metoprolol	Amantadine	Chlorpheniramine
Aripiprazole	Baclofen	Chlorpromazine
Azathioprine	Carbamazepine	Dicyclomine
(Most) benzodiazepines	Cetirizine	Levomepromazine
Bisacodyl	Cimetidine	Oxybutinin
Bupropion	Dosulepin	Orphenadrine
Captopril, trandolopril	Fexofenadine	Procyclidine
Carbidopa (Sinemet)	Nefopam	Promethazine
Celecoxib, lumiracoxib	Olanzapine	Propantheline

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Chlortalidone, some other thiazides	Prochlorperazine	Solifenacin
Citalopram/escitalopram	Paroxetine	Tolterodine
Codeine	Quetiapine	(Most) tricyclic antidepressants
Digoxin	Tramadol	Trifluoperazine
Diltiazem, nifedipine		Tizanidine
Dipyridamole		Trihexyphenidyl
Domperidone		
Entacapone, selegiline		
Fentanyl		
Furosemide		
(Most) glucocorticosteroids		
Haloperidol		
Isosorbide preparations		
Loperamide		
Loratadine		
Metformin		
Metoclopramide		
Morphine, oxycodone		
Mirtazepine, venlafaxine		
Pramipexole, bromocriptine		

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Ranitidine		
Risperidone		
(Most) selective serotonin reuptake inhibitor antidepressants		
Trazodone		
Triampterene		
Warfarin		

Group 1 drugs each score one point; group 2 drugs score two points; group 3 drugs score three points. The Anticholinergic Burden score is the sum. A total score >3 points is clinically significant.

Adapted with permission from Salahudeen, M. S., Duffull, S. B., Nishtala, P. S. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. *BMC Geriatrics*, 15(31). Copyright © 2015 Springer Nature. DOI: <https://doi.org/10.1186/s12877-015-0029-9>

Long-term drugs may be continued or temporarily or permanently stopped, depending on whether they are treating an immediately-evident problem (such as pain, or fast atrial fibrillation), causing problems (such as low blood pressure), or if taking oral medication is problematic. In the midst of delirium, it is reasonable to deprioritize long-term vascular preventative and bone-protection drugs, pending recovery.

Some 'non-diagnoses' may cause, contribute, to or exacerbate delirium, or cause symptoms similar to it, such as agitation or distractibility, in the absence of the full syndrome of delirium. It is unclear if these associations are truly causal, and if so, what the mechanism might be, or if delirium is caused by the underlying condition or associated treatment. Pain is strongly associated with delirium; delirium may be due directly to the pain, the condition causing the pain, or opiate analgesia. Likewise, sleep deprivation, constipation, and urinary catheterization are all associated with delirium, with the mechanism being causal, reverse-causal, confounded, or treatment-related. Whether causal or not, these conditions need to be explicitly sought and managed (investigated, cured, or palliated).

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Mimics and differential diagnosis

About half people over the age of 70 admitted to hospital are cognitively impaired, with 15–30% having diagnosable delirium. Of admissions, 10–15% are primarily due to ‘worsening confusion’ (Reynish et al., 2017; Pendlebury et al., 2015; Whittamore et al., 2014). Like any presenting symptom, accurate diagnosis is required to allow logical treatment and prognostication. While positive features of delirium should be identified, and diagnostic criteria confirmed (i.e. delirium is not a diagnosis of exclusion), it should be borne in mind that the diagnostic criteria include the caveat ‘not better explained by an alternative condition’. Alternative conditions must therefore be considered and excluded (Table 37.5).

Table 37.5 Mimics and differential diagnosis

Condition	Clues
<i>Vascular dementia</i>	Previous stepwise decline, or persisting new cognitive impairment after a stroke. Clinical or imaging evidence of cerebrovascular disease. Absence of specific features of delirium or concurrent acute physical illness. Failure to recover.
<i>Dementia with Lewy bodies</i>	Can be almost indistinguishable from delirium (fluctuation, including of alertness, delusions, hallucinations). Adverse drug effects common. Ascertain Parkinsonian features, longer-term problems, and decline, and recovery after treating concurrent physical illness. DAT scan if needed.
<i>Intoxication</i>	History of drug or alcohol ingestion, blood, or urine toxicology
<i>Coma</i>	Severe and persistent impairment of level of consciousness, neurological examination, and imaging findings
<i>Stroke, or brain tumour, especially aphasia</i>	Brain imaging. Can be difficult to assess. Stroke may cause delirium, or may represent a ‘better alternative explanation’.
<i>Post-ictal confusion</i>	History of seizures, rapid recovery

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<i>Rapidly progressive neurodegenerative conditions</i>	Index of suspicion, previous experience. Including CJD, PSP, CBD, DLB
<i>Functional psychosis</i>	Mental state examination, auditory hallucinations, systematized or mood-congruent delusions, overactivity in clear consciousness
<i>'Decompensation' of prior dementia</i>	Change of environment, loss of familiarity and routine, and discomfort or perceived threat in hospital can all produce changes in behaviour, sleep, and function.

CJD, Creutzfeldt-Jakob disease; PSP, Progressive supranuclear palsy; CBD, Cortico-basal degeneration, DLB, Dementia with Lewy bodies; DAT, Dopamine transporter.

General principles of management

The general approach of Comprehensive Geriatric Assessment (CGA) is required, including medical, functional, mental health, social, and environmental aspects (Ellis et al., 2017). Delivery of care is multiprofessional, requiring skilled doctors (usually a geriatrician and/or psychiatrist), general and/or mental health nurses, occupational therapists, and physiotherapists, with access to speech and language therapy, dietetics, and social work if needed.

The key elements of management are to:

- treat the underlying cause
- provide appropriate supportive care (physiology, hydration, nutrition, psychological, and emotional)
- maximize, maintain, or restore function
- avoid complications (falls, pressure sores, aspiration, deconditioning, injury or assault, post-traumatic stress disorder)
- engage families and other carers, explanation of unfamiliar phenomena
- wait; much delirium passes quickly (40% in 24h), but some recovers slowly (15% recovers between 4 and 26 weeks), or not at all (Cole et al., 2009).

People with delirium may be very ill; basic physiological and nutritional support is required to maintain body systems, while definitive medical treatment takes effect. This includes oxygenation, hydration, renal function, blood glucose, and heart rate control.

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The usual hospital ward does not provide a suitable environment for management or recovery of delirium (Jackson et al., 2017). They are unfamiliar, and disorientating (wards, bays, and rooms all look the same) with little privacy. They are often crowded, active, noisy places. Noise and activity often continue through the night, making sleep difficult. Patients can find these over-stimulating (noise and activity), under-stimulating (boredom), and overwhelming (incomprehensible or threatening). There are few opportunities for purposeful activity, exercise, or access to fresh air. Other patients with cognitive impairment, disinhibition, or displaying problem behaviours, such as calling out or interfering, provide further challenges. While individual practitioners have little immediate control over these, some may be avoided or mitigated (noise, opportunities for exercise, or activity), or process and environmental improvements can be advocated with management or hospital decision makers. Dedicated units are increasingly set up to address these and other system challenges (Goldberg et al., 2013; Flaherty et al., 2010).

All frail older people are at high risk of complications. Complications can prevent, undermine, or reverse recovery. Much of the benefit of specialized management is through the prevention, early detection, and aggressive management of complications.

Falls are a particular risk: physical illness, often on a background of dementia or other chronic disease, motor restlessness, autonomic instability (and low blood pressure), fear or paranoia, and impaired judgment all contribute to an increased risk of falling. Those who are hypoactive are at risk of pressure sores. Impaired swallowing may result in aspiration. Paranoia may result in assault or self-harm. Thorough risk assessment and action to reduce risk is required as part of a balanced and proportionate treatment plan; remembering that priorities may conflict, and preventing falls through inactivity or restraint is of little value if the result is deconditioning and immobility.

Delirium may result in incontinence. This should recover in parallel with delirium recovery, but comorbidities are frequent, especially incomplete bladder emptying, nocturnal polyuria, overactive bladder, cancer, and infection. These should be sought and managed. Most drugs used for managing overactive bladder are anticholinergic, and likely to worsen delirium, and so should be avoided. Trospium and mirabegron are the best options if needed. Urinary catheterization is indicated only for monitoring urine output in the critically ill, or for urinary retention. Catheterization is uncomfortable, provocative, and associated with complications (bladder spasms, infection, blockage, urethral trauma); and should not usually be used to contain incontinence, unless skin maceration is a problem.

Delirium is unfamiliar to the general population and many hospital staff. It often leads to dramatic, bizarre, or frightening changes that provoke bewilderment and anxiety. Family engagement is an important part of management. Families have information that healthcare professionals

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need (past medical and cognitive histories, how the acute problem developed, function and social support or care arrangements, home environment, routines, preferences, wishes, and values). Healthcare professionals have information that families need (explanation of the problem, treatment plan, and prognosis). Family members may want to help with sitting, occupation, or hands-on care, and should be encouraged to do so if willing and able. We need the advice of families in decision-making, care, and discharge planning. Pre-printed leaflets about delirium in plain English and other languages can help. Information on prognosis depends on context: while there is hope of recovery and restoration of cognitive and physical function, prognosis for both survival and recovery is rarely good, up to half may be dead within six months, and sometimes cognitive function does not recover. Families should be prepared for this. Such conversations may become discussions about end-of-life care.

Behavioural and psychological symptoms in delirium

Delirium includes cognitive change, delusions, or hallucinations in about half, and prominent emotional changes (fear, anxiety, depression, anger). These may result in behaviours that indicate distress (problem or challenging behaviours), such as calling out, agitation, aggression, resistance to care, unsafe attempts to walk, sleep disturbance, and anorexia. Managing delirium requires attention to mental health, psychological, and emotional care.

Plans cannot be made unless symptoms are ascertained, which is done by examining the mental state, observation, and obtaining reports over time from nurses, families, and other carers (especially about night-time). This includes explicitly assessing communication, understanding and expression, and psychosis. Hospital doctors vary in their ability to do this, representing a potential missed opportunity, and emphasizing the importance of liaison mental health services to support them.

Hallucinations are typically visual, formed (animals or people), and animated (moving), and may be distorted (incongruous, small, or giant) (O'Malley et al., 2008). Other sensory modalities may be involved, including tactile skin sensation (formication). Auditory hallucinations are unusual. Delusions are typically persecutory, involving the threat of harm. They are fleeting, fragmented, and changeable over time, rather than the more consistent delusional systems seen in other conditions. They are usually frightening, and associated with labile emotions, may result in expressed distress, attempts at defence (including aggression), or withdrawal. Also possible are illusions (real things appearing to be something else) and misinterpretations. Dreams may be vivid and frightening, and merge into daytime hallucinations. Communication impairment can make it hard to describe, share, or express these experiences; sometimes they have to be presumed from observations and behaviours. Often the behaviour (such as attempts to escape, reluctance to eat, or aggression during care) will be observed, but difficult to interpret without the corresponding psychopathology, and may be assumed

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to be wilful or 'part of dementia'. When assessing a person displaying challenging behaviours it is important to consider the possible presence of delirium, and examine the mental state for psychosis.

Physical illness, symptoms such as pain, constipation, or urinary symptoms, loss of ability, hunger or thirst, and separation from family and familiarity also evoke psychological and emotional responses. In addition, comorbid dementia, depression, anxiety, or other mental health problems are common. Together, the physical, mental, functional, social, and environmental elements provide a toxic mixture that can be threatening.

The philosophy of person-centred care was developed for use with people living with dementia, but the principles apply equally well in delirium, those with other vulnerabilities such as sensory impairment or intellectual disability, or at the end of life (Brooker and Latham, 2015). The first principle is of value or respect for the person with delirium: understanding their illness and its consequences, and not seeing these as wilful, nasty, or vindictive, or resenting their presence in a general hospital (Tadd et al., 2011). The second principle is to individualize care: including physical and mental health aspects, identifying problems and retained abilities, and taking account of sensory impairment (hearing, vision), personality, and preferences. The third principle is empathic understanding, seeing problems from the point of view of the patient. This is summed up in the axiom 'see behaviours as communicating distress or unmet need'. The healthcare professional's task is to identify the need or cause of distress. The final principle is to use relationships to bring comfort, inclusion, attachment, occupation, and to affirm identity. This requires a positive effort from the healthcare professional: to be friendly, encouraging, non-confrontational, and to avoid humiliation, infantilization, or embarrassment, using both words and body language (e.g. smiling, touch, posture). Language has to be adapted to account for deafness and communication impairment, and it is important to use clear and simple expressions, made with authority but acknowledging and minimizing anticipated difficulties.

A lot of the 'magic' of specialist practice in minimizing distress and difficult behaviour is achieved through the avoidance of problems, as much as the skill with which they are dealt. That is not to say that all problems are wholly avoidable: residual symptoms must be anticipated (through observation and care planning), tolerated (which may be the best approach, even to a risky or difficult situation), or managed (using talking, activity, or drugs).

The limit on this approach is the occurrence of immediate and serious risk to health or life. This will often take the form of episodes of aggression towards staff (for example, during personal or intimate care, or while redirecting from a risky situation), other patients or visitors (who are often vulnerable themselves), or to the individual (self-harm or falling). The occurrence of delirium is no different from other occasions of grave and immediate risk. In these cases, the situation must be rapidly

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appraised, other patients or visitors guided away from the incident, and attempt made to verbally de-escalate. An attempt should be made to identify the trigger for the problem, and address it if possible (such as pain or the need for the toilet). Physical restraint or separation may be required, and a rapid tranquillization regimen implemented (Harwood 2017).

Fortunately, most people who have an episode of delirium recall few, if any, details after the event. Some retain vivid and frightening memories, unable to distinguish or explain delusion from reality even many years after the event, despite insight and knowledge of what delirium is and does. Post-traumatic distress disorder can result (flashbacks, nightmares, anxiety, avoidance, isolation, and guilt). It is clear that delirium is highly distressing for some people. These have been better documented in critical care survivors, but distress from acute cognitive and perceptual disturbance can be a very prominent complication of the inpatient experience, particularly those living with dementia. 'Debriefing', explanation, and counselling may help: intensive care units now often follow-up patients to explore this.

Antipsychotics and other drugs

The role of drugs in delirium is complex. Drugs or their withdrawal may have caused the delirium in the first place. Other drugs may be used to treat acute or chronic illness, and these may cause or exacerbate delirium themselves (such as opiates given for pain). Drugs may also be used to try prevent or cure delirium, palliate delirium-related symptoms, or control behaviours.

Some trials have suggested that haloperidol might prevent delirium, or reduce its duration or severity when given in high-risk situations, such as hip fracture surgery, in advance of onset (Kalisvaart et al., 2005). However, subsequent trials have been disappointing, and a systematic review gives no support to this role (Neufeld et al., 2016).

A specific anti-delirious effect of antipsychotic drugs has been proposed (Meagher et al., 2013; Meagher et al., 2018). Historically, antipsychotic drugs have been used to 'treat' delirium. Nowadays, much lower doses are used than was once the case, and anecdotal experience suggests that low-dose, short-course antipsychotic prescription (such as haloperidol 0.5–1mg bd, or risperidone 0.5–1mg/d for five to seven days) can shorten the course of delirium. Alternatively, these cases may have been resolving anyway. Trial evidence mostly comes from intensive care unit settings, and is of uncertain applicability to frail older people in medical or trauma settings; however, there is little hard evidence to support efficacy of antipsychotic drugs in 'curing' delirium (Neufeld et al., 2016).

A logical use of antipsychotic medication in people with delirium would be to palliate psychotic symptoms, severe anxiety, or distress. Anecdotal evidence lends support to this practice, but trial evidence is lacking:

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indeed, there is evidence that antipsychotic drugs are ineffective. A sensible approach is 'trial and error': identify the target symptom, and choose a drug appropriate to control it, at a dose determined by body size, previous exposure to antipsychotic drugs, and intensity of symptoms, then reviewing for effect, tolerance, and adverse effects (in the case of delirium, daily or every few days). Over-sedation, extra-pyramidal motor effects, and risk of arrhythmias due to electrocardiographic prolonged QT interval leading to sudden death are the main adverse effects.

A final use of antipsychotic drugs is as a sedative in emergency control situations. In adult mental health practice lorazepam is now the preferred drug, but in delirium benzodiazepines are less effective and riskier in the light of possible paradoxical agitation, over-sedation, or risk of falls (apart from some specific indications). Antipsychotic drug doses tend to be higher in emergency situations (2.5–5mg haloperidol, delivered intramuscularly, every 20–30 minutes), in view of the need to achieve rapid control of a dangerous situation, with appropriate physical restraint, until control is achieved (Harwood, 2017).

There is no evidence to support use of pro-cholinergic drugs, or acetylcholinesterase inhibitors (Yu et al., 2018), and some evidence that these may cause harm.

In palliative care practice, haloperidol, levomepromazine (which is sedative and has analgesic as well as antipsychotic properties), or midazolam are often used, usually subcutaneously.

There are specific situations where benzodiazepines are indicated, especially alcohol withdrawal and delirium tremens. In opiate withdrawal, either provide supportive care alone, or restart an opiate and wean it down slowly. In some cases, clonidine may be indicated, though blood pressure needs close monitoring.

Delirium in the context of dementia with Lewy bodies or Parkinson's disease dementia represents an especial problem. Psychotropic drugs should be avoided, if at all possible. If distress or risk is severe, use lorazepam (0.5–1mg aliquots). These patients will often be given (or already be on) a cholinesterase inhibitor (oral donepezil or a rivastigmine patch).

Anxiety and low mood are very common, with a corresponding temptation to prescribe an antidepressant drug. There is little evidence to support effectiveness, and a theoretical risk of exacerbating delirium. Drug treatment is best avoided until the delirium has recovered; if distress is severe, a short-course of low dose antipsychotic might be tried, with appropriate review for effect and adverse effects.

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Persistent delirium

A third of delirium cases persist more than a month, a quarter more than three months, and 20% more than six months, most of which will never recover (Cole et al., 2009; Siddiqi et al., 2006). Persistent delirium represents a management problem; modern medicine operates at a fast pace, and a slow time-course of recovery conflicts with this model. Mental health services are cautious about delirium with its potential for severe underlying physical disease. Rehabilitation services are suspicious of mental health conditions, especially cognitive disorders with uncertain potential for recovery. Short-term care home placement can become a default setting, but without careful case-management this can easily become permanent, regardless of eventual recovery. Formal review by a geriatrician, community mental health team, or memory assessment service should be planned.

Persistent delirium requires careful on-going assessment and re-assessment. Possible causes include:

- failure to identify, or control the underlying cause
- failure to identify multiple causes
- recurrence of the underlying cause (such as an infection)
- a new intercurrent condition, complication, or drug adverse effect
- evolution of delirium into dementia ('delirium damages the brain')
- a mistaken diagnosis (decompensated existing dementia, progression of vascular dementia, or dementia with Lewy bodies)

As delirium resolves it changes; it often becomes less florid (fewer delusions or hallucinations, less agitation), but fluctuation and drowsiness may persist. The imperative continues to maintain or improve function (walking, continence, dressing, leisure or therapeutic activity), avoid complications, and relieve distress. Families and other carers should be regularly updated.

Delirium in care homes and community management of delirium

Delirium is frequently present on admission to hospital (prevalent delirium), and 'increased confusion' is a common presenting complaint. Those who are functionally independent at home with frailty or a degree of cognitive impairment (whether this is formally diagnosed or not) may decompensate in the presence of delirium or subsyndromal delirium, dipping below the threshold that allows them to manage in their own environment. Community prevalence of delirium is generally reported at less than 1%, with prevalence increasing tenfold for patients with coexisting dementia (Davis et al., 2013).

Dementia and frailty are both common comorbidities in care homes, and delirium is frequently seen in these settings due to presence of these as well as additional risk factors (pain, dehydration, constipation,

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polypharmacy, chest and urinary infections). Point prevalence of delirium in care home settings has been estimated at 33% and 14% for those with, and without dementia (McCusker et al., 2011; Siddiqi et al., 2010). Studies into delirium detection and prevention in care homes have provided estimates of incident delirium between 0.85 and 2.2 episodes per 100 person weeks—i.e. a 50-bed care home could expect roughly one to two new episodes of delirium a fortnight (Heaven et al., 2014; Teale et al., 2018).

Transition into hospital for patients in their own home or from care home settings where delirium is suspected may result in worsening of the delirium or increased distress due to moving from a familiar to an unfamiliar environment. This needs to be weighed up against the requirement for secondary care investigations and treatment.

Whether or not delirium can be managed in the community is dependent on a number of factors that form the basis of a risk/benefit assessment between healthcare professionals, patients, and their families or carers. Although these decisions should be made on a case-by-case basis, some points for consideration may include:

- Are the patient and their family in agreement with attempting to manage the patients in their own environment?
- Are the causes and precipitants of the delirium identified and can these be treated safely and effectively at home (a wish to remain at home should not preclude access to appropriate and necessary medical care and intervention, e.g. intravenous therapies, imaging)?
- Is 24-hour supervision required and available (i.e. is someone able to stay with the patient and monitor for features that warrant hospital admission)?
- Are there dangerous or risky behaviours that cannot be safely managed at home (e.g. night-time wandering, significant aggressive or violent outbursts, lack of awareness of hazards, e.g. gas fires, cookers)?
- Is specialist (secondary care) medical or nursing input required?
- Is there a strategy for regular medical review and a contingency plan if management at home is not working or in the event of clinical deterioration?

One strategy might be for rapid assessment in hospital to identify and treat factors contributing to the delirium aiming for early supported discharge home with ongoing input from community rapid response teams or virtual wards. Another is for initial assessment and management to be at home where 'hospital at home' schemes exist. Although managing delirium at home has theoretical advantages for patients, the efficacy, safety, and any health economic benefits have not been established through primary research.

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Special situations

Alcohol and drug withdrawal

Half of heavy alcohol drinkers will experience withdrawal symptoms between six and 24 hours after ceasing (craving, irritability, anxiety, tremor, headache, palpitation, nausea, and insomnia). Withdrawal seizures may occur between six and 48 hours after cessation, and often progresses to delirium tremens. Delirium tremens is a more severe variant, occurring in 5% of heavy drinkers usually three to ten days after stopping. It has physical and psychiatric features, including: visual, auditory or tactile hallucinations, illusions, and delusions; drowsiness; autonomic over-activity (tremor, tachycardia, sweating, high blood pressure, pyrexia); agitation, anxiety, or fear. Prevention is by tapering dose of oral long-acting benzodiazepines (over seven to ten days). Treatment is with intravenous benzodiazepines. High-dose parenteral B vitamins should also be given. Mortality is about 10%.

Wernicke's encephalopathy

This is caused by severe thiamine deficiency, typically in malnourished heavy alcohol users, or after refeeding someone who is chronically malnourished. The commonest symptom is delirium; other features include abnormal eye movement, nystagmus, cerebellar-type ataxia, and a long-term sequela, and Korsakoff's psychosis (persisting retrograde and anterograde amnesia with confabulation). Prevention and treatment are with intravenous high-dose B vitamins (gut absorption can be poor in alcoholism), followed by oral thiamine. Intravenous B vitamins must be given before any glucose-containing fluid, or a central lactic acidosis may be precipitated—worsening risk of Korsakoff's psychosis. Other aspects of 'refeeding syndrome' may also occur. Korsakoff's psychosis is especially disabling, often making independent living impossible.

Neuroleptic malignant syndrome (NMS)

This is a rare syndrome comprising delirium, with agitation, muscle rigidity, fever, and autonomic instability (tachycardia, incontinence, sweating, labile blood pressure). Plasma creatine kinase is greatly raised (often >10000U/l). It is caused by starting, or increasing the dose of, antipsychotic drugs, including atypical antipsychotics. It is hard to identify: the clinical picture looks like infection, which is much commoner. Treatment comprises withdrawing the culprit drug, and supportive care while recovery occurs over one to two weeks.

Hepatic encephalopathy

Caused by liver failure, hepatic encephalopathy is characterized by fluctuating confusion and drowsiness, lethargy, poor sleep, mood or personality changes, asterixis (motor 'flap'), and constructional apraxia (inability to draw a five-pointed star, although this is non-specific). It occurs in cirrhosis, although in some cases this is undiagnosed, and is

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often precipitated by intercurrent infection, electrolyte disturbance, gastrointestinal bleeding, or constipation. Plasma ammonia is raised, and EEG is characteristically (but non-specifically) abnormal. Jaundice may or may not be present. Treatment is with high-dose lactulose (which changes bowel bacterial flora), sometimes with broad spectrum non-absorbed antibiotics (rifaximin). Treatment can be dramatic and gratifying, but longer-term prognosis is poor, due to the underlying liver disease, although improved by abstinence from alcohol.

Autoimmune or inflammatory encephalopathies

Also rare, these are often dramatic or severe, but are potentially treatable. Features include drowsiness, delirium, seizures, psychosis, focal neurological signs, and involuntary movements, such as tremor or myoclonus. These diagnoses should be considered when no other likely cause of delirium is identified, or when there are atypical features such as seizures. They are caused by systemic or brain autoimmune or paraneoplastic disorders. Hashimoto's encephalopathy is associated with high titres of anti-thyroid peroxidase (anti-TPO) antibodies. Other autoantibodies are directed against neuronal membrane proteins such as anti-NMDA or voltage gated potassium channels. Limbic encephalitis is caused by anti-neuronal antibodies (e.g. anti-Hu), and is associated with lung and other cancers. Primary or secondary CNS vasculitis can also produce similar symptoms, usually associated with headache. CSF protein is raised, and there may be changes on brain MRI. Management requires specialist neurologist referral and high-dose steroid treatment.

Post-operative delirium

This is common among frail older people (and others) who have undergone hip fracture or joint replacement, open heart or abdominal surgery, or major trauma, but there is little fundamentally different about the causes or management. The underlying condition (trauma, intra-abdominal sepsis), anaesthetic agents, dehydration, treatment (opiate analgesia), medical comorbidities, or perioperative complications (such as wound or chest infection, heart attack, or stroke) can all contribute. Attention to preventative measures is important in these high-risk patients. There is evidence to support regional over general anaesthesia in preventing delirium. Collaborative management between surgeons and geriatricians reduces incident delirium (Marcantonio et al., 2001). Delirium occurs in up to 80% of ICU patients, and is increasingly recognized. Assessment is complicated by anaesthesia, sedation, or intubation, but tools such as the Richmond Agitation-Sedation Scale and CAM-ICU can be used to assist. Prognosis may be somewhat better than among general or geriatric medical patients, but later recall of symptoms and post-traumatic stress disorder can be particular problems. Some sedative agents (e.g. dexmedetomidine) are less prone to causing delirium than others.

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End-of-life delirium

Delirium may be almost universal at the end of life, due to the underlying condition or to treatment, especially with opiate analgesia and anticholinergic drugs used to control respiratory secretions. However, about half of cases may be reversed, especially if drugs or infections are the cause (Hosker and Bennett, 2016). Diagnosing the approach of the end of life can be difficult: people with hypoactive delirium often look like they are dying, and although prognosis after hypoactive delirium is poor, up to half may recover with appropriate treatment and support. Key management goals are the relief of distress, maximization of function, and open communication with patients and families. This can imply a trade-off: most people would prefer to remain conscious and sentient for as long as possible, but high doses of analgesia or sedation to relieve symptoms may compromise this. Distressing psychosis, anxiety, or agitation can be treated, usually in this setting using haloperidol, levomepromazine, or midazolam, but requires an open discussion about treatment options and goals.

Decision-making, judgment, proportionality, and compromise

There are several frameworks to guide decisions about what is the right thing to do, with overlapping legal and professional obligations, and cultural expectations. These frameworks divide into four main groups, although in practice we draw on all of them:

1. the consequences of an action (benefits and burdens, the expected good has to justify or outweigh any harm or risk)
2. rights and duties (in particular the right of autonomy, to decide for oneself, and the duties to use resources fairly and not to discriminate)
3. the disposition or intentions of the stakeholders (virtues)
4. the need to maintain open and trusting relationships.

Decisions may be about medical treatment, the adoption of end-of-life care, restrictive or drug treatment to treat behavioural and psychological symptoms or maintain safety, the taking or avoidance of risks, or decisions about returning home or moving to a care home.

The problem in delirium is that cognitive impairment can impair mental capacity to make decisions (the ability to understand, retain, and use relevant information to a decision, and communicate that decision). In this situation decisions may be made by a proxy (in the UK, a holder of a power of attorney, or court-appointed deputy), or by assessing 'best interests' (which takes into account the previous and current wishes and preferences of the individual, and of the family or friends of the patient). Added difficulties are that delirium, and mental capacity, can fluctuate, and recovery can be slow or uncertain. It is easy to make a wrong decision, or make an irreversible decision too soon.

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A patient with delirium may misunderstand the purpose of routine observations, even though these are required to detect deterioration. As a consequence, this attention may be seen as threatening, or may disturb the patient's sleep. Attempting to prevent a patient from falling often leads to them being immobilized in a bed or chair, which can then result in confrontation when the patient attempts to get up, and denial of opportunity for them to exercise, regain function, and avoid deconditioning. Pressure area care may involve alternating pressure mattresses, which can be uncomfortable and prevent sleep, and regular (two-hourly) turning, which also disturbs sleep. Low molecular weight heparin injection to prevent venous thromboembolism can be painful and an opportunity for confrontation, while distracting nurses from psychosocial care. In managing delirium individualization is important; delirium pathways must guide best practice while allowing for this.

Being aware of these pitfalls can help. Open communication, and shared decision-making (setting out the options, the pros and cons of each, and agreeing a process to reach consensus) are needed (Coulter and Collins, 2011). Difficult decisions may take time to make. In the face of uncertainty, keeping options open is wise. Try to maintain relationships even in the face of disagreement.

Modern hospital medicine emphasizes 'rescue' (identifying rapidly deteriorating patients for critical care intervention), 'safety' (avoiding healthcare-associated harm), and 'pathways' (standardizing care to achieve efficiency). This sits uneasily against the needs of complex and frail older people, especially those with delirium or other mental health problems. 'Risk enablement' or 'recovery model' approaches emphasize positive risk-taking and accepting failure with the goal of maximizing function and inclusion. Ideally, these issues are discussed within multiprofessional teams, and with families, albeit time-consuming and involving difficult (or impossible) judgment calls.

Management of delirium calls for skilled staff, with nurses drawing on expertise from both general and mental health practice, with appropriate education, right attitudes, in sufficient numbers, and with medical, nursing, and management leadership that appreciates complexity, and the value of professional judgment and shared-decision-making.

Outcomes from delirium

General outcomes

Delirium is clearly associated with increased mortality, with an approximately two-fold increased risk of death (95% CI 1.5–2.5), even after adjusting for chronic comorbidities and burden of acute illness (frailty) (Dani et al., 2017; Eeles et al., 2012; Witlox et al., 2010). Why this should be the case is not obviously clear other than to highlight that when the burden of acute and chronic precipitants results in delirium, then other things being equal, those patients are likely to be nearer death.

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Delirium is associated with adverse in-hospital patient safety issues (Reston and Schoelles, 2013). This includes inpatient falls, dehydration, poor nutritional intake, aspiration pneumonia, pressure sores, increased length of stay, increased need for one-to-one care, and increased rehabilitation needs. Delirium is associated with a twofold increase in the rate of institutionalization (Pitkala et al., 2005; Bellelli et al., 2008; Bickel et al., 2008). These outcomes therefore come with substantial health and social care costs. There are several estimates available from high income healthcare settings. In the UK, it is estimated that a single episode of delirium complicating inpatient admission costs £13,000 (Akunne et al., 2012). The total annual cost of delirium in the US been estimated to be at least \$38 billion (Leslie et al., 2008). This is consistent with other health economic analyses undertaken in Australia (Pezzullo et al., 2019).

Long-term cognitive outcomes

One recent focus of epidemiological studies of delirium has been the investigation of prospective associations with worsened cognitive decline and incident dementia. The central question has been to understand if delirium is simply unmasking unrecognized dementia, or if delirium itself could lead to chronic cognitive impairment. Studies in hospital cohorts have suggested a strong association with dementia at follow-up (OR 12.5 (95%CI 1.9–84.2)) (Witlox et al., 2010). However, this observation is problematic for two reasons. Firstly, there may be a selection bias insofar as not all delirium cases necessarily present to hospital and therefore the observed association may be skewed by more severe delirium. Secondly, the association may be confounded by unrecognized dementia, that is, cognitive deficits observed a follow-up may have in fact been present before delirium. Nonetheless, the notion that delirium could be associated with prospective, step-changes in cognition is plausible from clinical experience and sometimes families report that a relative is ‘never the same again’ after having delirium. Also, it is apparent that not all individuals fully recover from delirium, though how such a persistent delirium might evolve into a chronic dementia has not been well characterized.

Several cohort studies have tried to address this by aligning a retrospective diagnosis of delirium with trajectories of cognitive decline delineated through longitudinal follow-up of cognition. Although these studies vary in terms of setting, age range, outcome measure, and delirium ascertainment, delirium is consistently associated with accelerated cognitive decline, months and years beyond the index episode of delirium (Fong et al., 2009; Gross et al., 2012; Davis et al., 2014; Davis et al., 2012; Tsui et al., 2018).

There has been some attempt to understand these trajectories in relation to underlying dementia pathology. Because the entirety of described clinical (e.g. age, sex, education) and pathological (e.g. amyloid and tau protein) factors account for only 50% of dementia risk (Matthews et al., 2009), it is reasonable to consider if delirium accounts for some of this

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unexplained variance. In the few studies where there are measures of cognitive decline, delirium, and neuropathology, it appears that delirium is *not* associated with higher levels of any given dementia neuropathological marker (e.g. amyloid plaques, Braak stage) but evidence of delirium in the final years before death may make the cognitive expression of these pathologies more evident. Even if delirium does account for some of the variance between pathology and cognition in dementia, there is as yet no evidence that delirium interventions have any impact on secondary prevention of dementia (Teale and Young, 2015), though this strategy clearly merits systematic investigation.

Uncertainties and future directions

While there has been general progress in delirium research, much of it has had insufficient impact on patient care. There even remain fundamental questions on the nature of delirium, with uncertainty as to whether it is too heterogeneous a construct, or whether there could be a unifying pathophysiology. Nonetheless, some speculations on the future of delirium research may be possible.

Pathophysiology

There is no doubt that more experimental work is required, but establishing valid cognitive and behavioural animal models to test possible hypotheses has not been straightforward. There is likely to be a range of existing animal models in fields relevant to delirium, but not known to delirium investigators. Examples might include neuroinflammation in sepsis, small vessel disease in the blood-brain barrier, and microbiome impact on encephalopathy. Experimental researchers in these fields may be unaware of the clinical construct of delirium, leading to missed opportunities for translational collaboration. Ultimately, there is a need for an infrastructure to engage and cross-fertilize with experimental researchers in a range of fields. The eventual aspiration would be the development of robust experimental systems that might be able to dissect out pathophysiological pathways that could be targeted for specific delirium therapy or to mitigate some of the adverse sequelae.

Neuropsychology of delirium

Most clinicians approach delirium as primarily a disorder of *cognition*. However, emphasis is increasingly on delirium as a disorder of *arousal* (which in itself should be considered to on a continuum with *inattention*). This has implications for the construction and design of delirium assessment tools where quantifying change in arousal should be as important as demonstrating specific cognitive deficits. Acute illness, drugs, degree of prior cognitive impairment, and superimposed delirium all interact to affect level of arousal. Future research must seek to understand the extent to which each has an impact on cognitive and functional outcomes. With regard to the plurality of available assessment scales, research is needed to assess how the diagnostic accuracy varies

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with setting and degree of training. Specifically, tests to detect delirium in the context of comorbid dementia need to be better established.

Considering delirium in the context of frailty and multidisciplinary care

At present, much of the focus on delirium care is on the acute precipitant. However, of equal importance is the recognition and management of frailty that commonly accompanies delirium. Highlighting this leads to a wider consideration of the multidisciplinary aspects to delirium care, which have received hardly any research attention. For example, which physiotherapy-led mobility interventions might reduce delirium duration? Is there a role for clinical psychologists to develop post-delirium recovery programmes? Are there subtle linguistic or paralinguistic deficits that might lead to early detection by a speech and language therapist? How common is bulbar dysfunction in hypoactive delirium and how should this be safely managed? Which nurse-led family education programmes could prompt earlier presentation? Taken together, it becomes clear that there are many opportunities to improve multimodal aspects of delirium care if research can leverage the skillset of the multidisciplinary team.

Improving healthcare systems

The public health impact of dementia is becoming increasingly prominent. Some of this has arisen through aligning delirium with dementia care in acute hospital. Crucially, studies demonstrating that delirium care is cost effective will be a potent driver to change. Yet, there remains a general lack of integration of delirium care across primary, secondary, intermediate, and social care. For example, delirium follow-up clinics are by no means routine. Without doubt, if interventions for delirium can be shown to lead to secondary prevention of dementia, this would lead to a wholesale change in how acute care for older people is organized, with a major focus on preserving cognitive function.

Raising public awareness

Despite increasing awareness and expertise on delirium among health professionals, there have not been any large-scale attempts to engage the public on delirium. The term is hardly used among patients and families. Greater efforts from the scientific and clinical research communities, perhaps in conjunction with ageing-related third sector organizations, to increase public understanding are vital. Such efforts will be rewarded by highlighting need for research funding and step-changes in standards of care.

Conclusion

Delirium is a distressing and expensive clinical entity that is known to also influence cognitive and other health outcomes. It should be considered as a marker of acute brain injury commonly precipitated by a peripheral or systemic acute event. Both level and content of consciousness are important to assess. However, many of its features

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have not been fully characterized, formal measurement is still problematic, and underlying mechanisms are largely unknown. Given that it is potentially preventable and treatable, substantial clinical efforts should be directed to its management in its own right. Treating delirium hinges on addressing the underlying cause, brain optimization, and being vigilant for distress and providing symptom relief as needed.

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The experience of depression: Anonymous

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Introduction

I have had episodes of depression intermittently all my life. As they are individual to me, I've supplemented my experience with an informal browse over other people's descriptions on the Internet. I've chosen to write anonymously, not because there are shocking revelations, but because I want the chapter to focus on the content rather than the author. You may still be tempted to try to identify me (I probably would in your situation!). If you do (and it is probably not difficult) please respect my privacy.

Context

I was the first and only male of four siblings. My father was a doctor and my mother a teacher. Both, in their very different ways, set me very high standards, built around good behaviour, modesty, and service, whilst eschewing greed and complaint. I think I was naturally bumptious and

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presumably recognized as bright because my mother often made the point that I shouldn't get big-headed. Religion was a big factor for my mother, who essentially lived her life on the basis that it was wrong to seek pleasure if there were people in the world worse off than oneself, and she did indeed devote herself to myriad good causes. My father was a quiet man who worked tirelessly and unconditionally for his patients. They were widely recognized as exceptional people and community role models. Living up to their standards was going to be hard!

My parents wanted the best for me, and at the time they thought that meant private education. So, from age ten, I was a boarder at a pleasant enough prep school, followed by a public school that I hated. I think the experience of not being at home for more than 50% of the time left me rootless and without a sense of belonging. Dormitory insomnia meant that, at age ten, I started a lifetime of intermittent, then continuous, use of sleeping pills. At my public school, in particular, the first half of each holiday was pleasant but followed by a period of increasing gloom and apprehension at the prospect of a return to school. In retrospect these were depressive episodes; likewise, the sense of vulnerability I associated with spring was probably Seasonal Affective Disorder (SAD). Previously a devout Christian, I gave up on religion, never to be quite forgiven by my mother, judged by her non-verbal communication. I became rebellious and anti-establishment. This change was emblematic, I now think, of a more general suspicion and questioning of received wisdom. Above all, I felt trapped in an environment I did not like. If I lived my life again, I would have loosened the stiff upper lip, mandated by values of the time, and left that school.

Questioning received wisdom, however, served me well at university, where thesis and antithesis were the stuff of life. This was one of the happiest periods of my life. Unfortunately, going to medical school felt like entering a time warp into an isolated world based on class and privilege with an unstimulating environment and a curriculum based on largely pointless rote learning. It felt like regressing to my school days. I was enmeshed in the establishment that I felt opposed to, which made it hard to form strong bonds of friendship with other members. Maybe, this was also a time to drop the stiff upper lip and change.

My career was seen by others as reasonably stellar. Whilst I now accept this intellectually, I still don't really own that experience, emotionally. It felt to me like a stressful time, marked by anxiety and indecision. I let many life changes to chance. In the short run, fate felt more comfortable than personal choice and commitment.

Experience

I don't know how many times I have been depressed and I don't have a particularly detailed memory, possibly because I unconsciously suppress memories of bad times. It is usually associated with a personal or professional crisis. An early sign is a feeling of deep visceral tension in

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my lower abdomen, associated with untargeted free-floating anxiety, formless feelings of guilt, and a nameless sense of impending doom. Internet posts that refer to feelings of panic are probably describing the same experience. It is said that depression is living in the past whilst anxiety is living in the future, but I think a feeling of apprehension about the future is a common component of the depressive experience. As well as this autonomic and emotional side, there is also an intellectual one. Well or ill, I have an ongoing internal monologue, predominantly evaluating what could go wrong with any situation, and the analysis becomes more pessimistic and questioning of certainties when I am depressed. When I am well, questioning of certainties has served my career well. However, when depressed I wish I could switch the pessimistic voice off.

With depression, life becomes colourless. Nothing gives pleasure or satisfaction so it becomes difficult to stir myself to any activity. The ruminating internal voice tries to assess routes back to pleasure, meaning, and enjoyment and finds them wanting. I know what activities (exercise, socializing, outings, etc.) should lift my mood, but it is an effort to initiate them and they don't work. Feelings of profound regret are common. This is well expressed by one of the Internet writers who said: 'Depression is sadness for times gone and chances never taken. It is missed opportunities and a missed future. It's missed friends.'

Churchill is well known to have called depression his black dog and it seems that others animate the experience similarly. Susan Calman writes of the crab of hate sitting on her shoulder. Nothing like that applies in my own case. Depression for me is the dark skies and looming catastrophe of Mordor. I can think of two major crises when the associated weather was just like that. One insight I have gained from writing this chapter is that the Sauron presiding over my Mordor is the dark, saturnine, cane-wielding headmaster of my school.

Consequences

When I am well, I work hard and indeed have the reputation for almost inexhaustible reserves of energy (don't call me manic depressive!) and significant creativity. When I am ill, accumulating commitments continue to mount as I slow down. I become inarticulate. Life goes on hold, and meetings, social events, travel, and engagements are cancelled. Mental capacity clouds over and seems to be associated with nasal congestion and a thick head. I cease to function professionally and I have lost leadership positions, papers, and grant opportunities because I am, for a while, incapable of meeting the standards required of me. When depressed, I have forgotten about important speaking events but, by the skin of my teeth and with as little as 12 hours' notice, I have persuaded colleagues to stand in (with hearty thanks to anyone who works out who we all are)!

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This is when personal and professional catastrophes occur, some causal, some consequential. The impending sense of doom becomes reality. The pessimistic internal voice is vindicated. Indeed, bad developments feel like prophecies foretold. I can think of two crises which overwhelmingly felt as if they were the concrete manifestation of the catastrophe that had hung over me all my life, the inescapable exposure of me as a fraudulent impostor. So the sense of foreboding is corroborated and reinforced. I become distant to my family and friends, but I also regress and develop childish dependence, which only makes the gulf between us worse. I don't often cry, but when I do it is explosive and prolonged. I feel rejected. I have never harboured thoughts of suicide. The violence of the death that would be effective frightens me. I feel for those with depressions that are severe and am thankful that mine is only moderate in severity.

Causes

As a (hyper)critical person, I have been suspicious of the idea of personal trauma as a cause of depression. Being a victim, I used to argue, is an easy self-indulgent alternative to finding a more honest answer and being big enough to deal with it. This perfectionist version of personal truth has also made me suspicious of the therapeutic notion of developing a positive personal narrative. However, dear reader, you are probably sufficiently far ahead of me to see I was wrong and to guess where all this may have come from.

There were three big influences. I was a brainy child, but didn't realize it and my parents discouraged big headedness. So when I got scholarships and awards, I developed a severe case of the impostor syndrome. In this state, you are convinced that a mistake has been made and you will be shown up to be a fraud. You feel vulnerable so you work harder, so the fraud is not noticed. This is counterproductive because it makes you more successful and acclaimed, so the sense that you are an impostor intensifies and you work harder still!

Being brainy landed me in classes with boys two years older than me, and this had two consequences. Being relatively immature, I struggled to understand and fit into their world. Isolated in an all-male boarding school limited the outlets for my new testosterone-driven adolescent impulses. Overall, an important piece of social learning did not happen, leaving me with permanent feelings of social inadequacy. I feel I am stuck in an immature phase in which gaining approval from and pleasing others is the dominant driver of my professional and personal activity.

So far so common, as I judge from others. The third consequence of these adolescent experiences seems not to be shared by many others.

Conditioned to see myself as a younger child in an adult world, I see virtually everybody as being older than me, even if they are 30 years my junior: a sort of anorexia nervosa of age estimation. I try to imagine how others younger than I am see me, particularly in the context of having a high professional status, but I cannot in any meaningful way. Other

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people find this hard to understand. Now that I am old, it is quite disorientating to see those who I had misperceived as older than me still active and indeed still alive!

The analysis of the unconscious effects of early life experience may sound trite and obvious, but it took many years to consider it relevant and many more to accept it emotionally!

In terms of transactional analysis, I am the child at the bottom of the chart! I think this feeling of inferiority has actually helped my clinical career, by mitigating some of the stereotypes that arise in the consulting rooms. The child sitting in the authority figure's chair may be seen as a more approachable equal. At other times, the child gets hurt by the actions and attitudes most commonly of competitor colleagues who pitch at the powerful stereotype.

Treatment and support

Along the way, I have seen counsellors, psychiatrists, and psychologists, starting with referral to a priest (me still an atheist!) whose approach was to lie on the floor and meditate! Talking through a crisis is usually helpful. Naturally, some sessions have been more helpful than others. I am not attracted to Internet chat rooms or fora, as their unfiltered comments are often incoherent, angry, or wrong and can feel aggressive, threatening, and indeed actively depressing when one's mood is low. It is also a great thief of time. However, I was interested to take a focused snapshot of the experience of depression, as posted on the Internet, where many posts assert that the worst thing to be told when depressed is to 'cheer up'. I recall colleagues trying to help by sketching out a positive pathway out of the pit. This can feel like a slightly impatient cajolement, especially in those with time pressures in their own life. Another Internet theme is the importance, at a time of crisis, of active listening by the therapist or counsellor. That would also be top of my list. Early on, I think active listening may be most effective if devoid of other agendas like diagnosis (only an approximation to individual experience) or therapeutic planning.

Then a time comes when one tries to think oneself out of the gloom. At this stage, I believe there can be a need for some at least partially didactic input from the therapist. There is often a reluctance to do this. I can see that encouraging a return to normality requires the patient to own the decisions, but when one is starting to do this whilst still vulnerable, some signposting from an external individual who probably has more insight would be helpful. It may be a bit demanding to ask for active listening transitioning to active planning by the therapist on behalf of the patient. All in good time!

Experience vs pharmacology

Most new consultations were triggered by a crisis. So what did I hope to gain from them? The truth is I didn't know at the time. I needed to unburden myself. I was certainly not seeking comprehensive self-analysis

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and indeed for a long time was implicitly sceptical to this approach. So I have taken psychoactive drugs for a long time. Tricyclics did not work. Of the SSRIs, paroxetine was most effective. They make the internal voice more positive. I was started on mirtazapine (fabulous dreams!) by my GP. I think he has forgotten it was to enable me to wean off the paroxetine. I doubt this would be possible and I feel in a better and more consistent mood than I have for a long time, so I am keeping my head down! If I'm addicted, so be it.

Many Internet posts are strongly hostile to psychoactive drugs. Those in favour are generally less strongly expressed. This polarization of opinion is not surprising as it interfaces with a broader view of what it is to be human. I can see pharmacology and experience as two windows on the same phenomenon.

Old age psychiatry

I was initially apprehensive about referral to an old age psychiatry service. Would it not be an exercise in assessment for Alzheimer's disease? I rapidly realized this caricature is misplaced. Depression is common in old age and usually has a long development in early and middle life. I'm wary of assessing one's own self-esteem, but I suppose mine is low. After all, what's not to dislike about an emotionally immature person, unsure where he belongs, who was not brave enough to break free of his personal chains and choose Robert Frost's road less travelled, and whose success in life was built on accidental by-products of his personal weaknesses? The accidental professor! I have been even more wary of describing the formative events I describe as traumatic. Compared to child sexual abuse, it seems pretty mild, but as I have grown older with greater insight it seems capricious not to acknowledge a probable relationship. As I've aged, I have, like most people of my age, dropped the impetus to change, and started to accept myself and my psychological warts! It is just my story and writing it at this stage of my life has been therapeutic!



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Depression in older people

Chapter: Depression in older people

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What is depression and how common is it?

Depression seems to have become a Humpty Dumpty term, one that can mean whatever the speaker wants it to mean—transient sadness, misery due to stress, a collection of symptoms on a check-list, or a clinical syndrome. It is easy to forget this important truth and proceed as if findings from research (predominantly on DSM- defined (unipolar) major depressive disorder (MDD)) can simply be applied to anything labelled ‘depression’. DSM MDD is diagnosed when someone has one or more major depressive episodes, which are episodes of depressed mood and/or anhedonia plus at least four other key symptoms from a list of nine (total of at least five symptoms). Its prevalence has been repeatedly reported at 1–3%, a rate similar to that in younger adults (Beekman et al., 1999).

Importantly the DSM-5 criteria are not simply a checklist of symptoms, since the DSM manual details these clinical features, which need to persist over at least two weeks, and this collection of symptoms needs to

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produce clinically important impairment in everyday functioning. An important change from DSM-IV is the removal of the bereavement criterion for MDD. Previously, DSM discouraged the diagnosis of MDD following the death of a loved one, recognizing that depressive symptoms for more than two weeks are common following bereavement and do not necessarily signify illness. Although the concern to encourage identification and treatment of depression is understandable, the removal of the bereavement criterion may encourage the medicalization of normal grief. And more widely it may discourage clinicians from placing someone's depressive symptoms in their personal and social context. That is, depressive symptoms precipitated by grim circumstances need to be understood as related to these and managed accordingly. A diagnosis of DSM MDD should not lead straight to the prescription pad. There is a wide range of severities of MDD and although MDD is widely regarded as 'severe depression', many people with milder illnesses meet the criteria and may be managed without medication (indeed DSM-5 MDD has mild, moderate, and severe subtypes, and severe with psychosis).

The UK NICE Clinical Guideline on the management of depression in adults (CG 90) emphasizes that duration and disability due to depression should be carefully assessed when determining the appropriate management (which then follows a rational stepped care approach) (NICE, 2009), in which psychosocial interventions are advocated for milder and more transient episodes and medication encouraged for persistent and/or moderate to severe episodes (which should approximate to moderate and severe DSM MDD).

The other main category of depressive disorder in DSM-5 is persistent depressive disorder (dysthymia), which is diagnosed when depressive symptoms persist for over two years without meeting criteria for MDD or where someone with a previous episode of MDD has persistent symptoms. DSM-5 persists in its current version (DSM-5) in not recognizing a 'minor depressive disorder', which would best capture many people with 'depression' in primary care whose most appropriate treatment following NICE's approach is psychosocial. This omission is, apparently, due to American insurance companies not supporting any condition deemed 'minor', rather than for good clinical reasons (Shorter, 2013).

Minor depression would also seem to capture a large group of older people with less well-defined depressions, sometimes termed 'subsyndromal depression'. This term derives from the fact that individuals with such depression fall short of the full criteria for MDD, but they do so for different reasons: some have partially responded to treatment; others have partially spontaneously recovered; some have never attained MDD status and wax and wane in symptom severity and frequency; some have chronic, low-grade symptoms. Studies of these ill-defined categories, essentially assessing the presence of substantial depressive symptoms yield prevalence rates about three times higher than for MDD (Meeks et al., 2011). However, it should be emphasized that

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symptom duration and related disability are crucial for informing management.

The next broad category of depression in older people is depression comorbid with other illnesses. Depression is recognized to occur at high levels in people with physical illnesses generally (Goodwin, 2006) but, as might be predicted, it is especially associated with brain diseases. It occurs in 20–40% of people with Parkinson's disease (PD) (Lieberman, 2006), in 25–50% of people with dementia (Ballard et al., 1996a), and about a third of people after stroke (Gaete and Bogousslavsky, 2008). Related to this is that rates of depression in older people in residential care facilities are about three times higher than in the community (Blazer, 2003).

It seems clear that, unlike dementia which shows a clear association with increasing age, MDD does not increase with age and, if organic disorders such as dementia are excluded and disability is controlled for, depression more broadly does not appear to change in prevalence with age (Blazer, 1999; Jenkins et al., 1997; Roberts et al., 1997). Females are still more likely to be affected than males, though this sex difference may narrow with increasing age (Bebbington et al., 1998; Jorm, 1987). The lack of association with ageing contradicts widespread views that ageing itself is a risk factor for depression.

Clinical features of late-life depression

It has often been suggested there is a different symptom profile characteristic of depression in the elderly. Evidence for this is limited and, reviewing the literature, Baldwin (1994) concluded there was little evidence for phenomenological differences between older and younger depressed patients. However, certainty is hampered by much of the research being done using DSM criteria for MDD, which arguably might conceal differences in symptoms patterns in younger and older people; such findings of no differences may therefore be somewhat self-fulfilling. Certain clinical features may be more characteristic of older people, but this is not necessarily due to depressive illness. For example, the concept of 'masked depression', in which elderly people complain of somatic problems and not low mood, has not generally been supported and the idea may reflect a cohort effect, with older people not wishing to bother their doctor, or only do so for physical symptoms (Baldwin, 1994).

Some studies have directly compared symptoms in older and younger adults with depression. One reported the older group to be more severely depressed and to have significantly more delusions, agitation and appetite loss (Brodaty et al., 1991), and the other also found older patients to be more severely depressed and to have more psychomotor disturbance, psychosis (both hallucinations and delusions), and melancholia, and also more appetite loss and weight loss (Brodaty et al., 1997). Other studies report an increase in somatic complaints, insomnia (Husain et al., 2005), and hypochondriasis (Gurland et al., 1976). Other

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symptoms such as irritability, hypersomnia, and pessimism may become less frequent (Husain et al., 2005). Other studies have, however, noted few age-related differences (Blazer, 2003). Study bias is likely to play a role in such studies as they emanate from specialist units and it is not clear how well they generalize to other situations and cohort biases may also be present (that is, older people report symptoms differently). The one type of clinical feature which is clearly more prominent in older people with depression is cognitive impairment. While cognitive symptoms are not themselves diagnostic symptoms of depression, they are a critical element to examine when assessing older people with depression and we discuss later the complex relationship between depression and cognitive impairment.

Early onset and late onset depression

An alternative way to approach depression in older people is to distinguish depression beginning earlier in life (early onset depression, EOD) from depression presenting for the first time in older people (late onset depression, LOD). Different studies have employed different age cut-offs but LOD is most commonly, but arbitrarily, defined as a first episode after age 60. These studies all assume that people accurately recall age at depression onset, which is unlikely to be true. Although it is often thought that LOD has a different symptom profile, a systematic review found this is not the case (Grayson and Thomas, 2013).

In summary, the symptoms used for diagnosing depression remain the same in older people, which makes detecting any possible differences in symptoms difficult. It is not clear that any specific depressive symptom occurs more or less frequently in older people, although in selected hospitalized subjects, psychotic and psychomotor symptoms may be more common. The only symptoms which are more severe in late-life depression are cognitive impairments, but these are not used for diagnosis and usually specialized tests are needed to identify them.

Assessment of depression

Chapter 9 discusses assessment in detail, and therefore only key points relevant to depression are discussed here. A major difficulty in assessing depression in older adults is comorbidity (that is, depression coexisting with physical illness). Both DSM and ICD take an aetiological approach, so that people whose symptoms can be attributed to physical illness are not diagnosed as having depression by these criteria. While this appears conceptually reasonable it is often difficult in practice for a clinician to determine whether a symptom, such as insomnia, is due to depression or the physical illness, such as discomfort arising from shortness of breath. A careful history, paying attention to the onset of depressive symptoms in relation to the comorbid illness, is essential but frequently it will not be possible to attribute symptoms to depression with much certainty.

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This difficulty in deciding whether to attribute a symptom to the physical illness or depression is compounded by the recognition that frequently older people with depression complain of somatic symptoms rather than low mood. Pain complaints in all ages are a well-recognized presentation of depression (Katona et al., 2005). These are typically non-specific, including headache, abdominal pain, and back ache, and may be multiple. The high prevalence of pathologies potentially causing such pain in older people, e.g. lumbar osteoarthritis, makes it especially difficult to distinguish physical from psychological causation and a mood-related exacerbation of such pathological pain is common. In practice, complaints of pain and other somatic symptoms in the absence of a clearly attributable physical cause should raise the strong suspicion of depression and lead to appropriate mood related questions.

Similarly the emergence (or significant worsening) of anxiety or obsessional symptoms in an older adult should lead to questions about mood as the onset of a pure anxiety disorder is unusual in old age but it has long been recognized by clinicians that anxiety, agitation, and obsessional symptoms are frequent features of depressive illness later in life (Post, 1972). Late-life depression can present as an anxiety disorder and lead the unwary to not recognize depression and treat this appropriately. Deliberate self-harm may be less frequent in older people but it should always lead to careful investigation for depression (or other mental illness) because such acts are more likely to be associated with mental illness and to presage a more serious suicidal act (Manthorpe and Iliffe, 2010). Older men (>75) are the group at highest risk of suicide and most older people who commit suicide have major depression (Manthorpe and Iliffe, 2010). As in younger adults, it is precarious to try to gauge the seriousness of the act from its objective level of risk and close supervision, usually as an inpatient, and treatment is required in such cases (this important topic is considered in more detail in Chapter 40). Behavioural change in an older person may also be a consequence of depression. In such cases it is well recognized that a careful cognitive assessment is needed since the behaviour may be an aspect of an early dementia, but mood assessment is also important especially where no evidence of cognitive decline is evident. A key behavioural change to consider is the emergence in later life of alcohol dependence, which may be a manifestation of a maladaptive strategy for dealing with a depression.

Cognitive impairment, depression, and dementia

Perhaps the most important clinical difference in depression in older people is that cognitive impairment is more prominent. The complexity of the relationship of depression to cognitive impairment and dementia is well known and four main relationships between them may be recognized (Fig. 39.1; Thomas and O'Brien, 2008).

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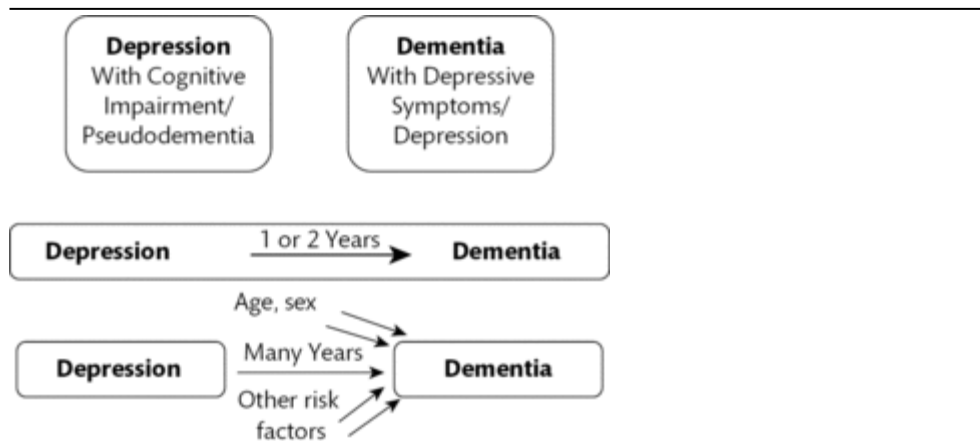


Fig. 39.1

Four types of relationship of between depression and dementia.

Depression in pre-existing dementia

People with dementia commonly have depressive symptoms, with one review reporting a prevalence of 42% in Alzheimer's disease (AD) (Zhao et al., 2016). Most studies are in AD but the few studies examining subtypes have found depression is more frequent in vascular dementia (VaD) and dementia with Lewy bodies (DLB). For example, one study reported major depression in 10% of subjects with AD but 29% with VaD (Reichman and Coyne, 1995) and major depression was found significantly more often in DLB (33%) compared with 13% in AD (Ballard et al., 1999). There is marked variation in reported figures due to the use of different samples and assessments, but also a difficulty in assessing major depression arises from the aetiological approach to diagnosis in DSM, since distinguishing symptoms due to depression from those due to dementia is inevitably inexact and subject to variation between raters. One consequence is that specific criteria have been proposed for diagnosing depression in the presence of AD (Olin et al., 2002), which include symptoms not emphasized in ICD or DSM, such as reduced positive affect, social isolation, and withdrawal.

Depression as a prodrome of dementia

Major depression, especially when presenting for the first time in later life (LOD), can also turn out to be a prodromal presentation of a dementia. In secondary care the conversion rate was reported as four- to fivefold greater than in non-depressed elderly (Alexopoulos et al., 1993a), while in a primary care study it was found to be one- to twofold increased (Lenoir et al., 2011). Thus, those presenting for the first time with depression in old age should be carefully assessed for cognitive and functional impairment, with a view to trying to determine whether the extent of such impairments is consistent with the severity of mood symptoms. In some cases, it can be recognized that this is not the case

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and more detailed neurocognitive and neuroimaging assessments may be indicated to identify a dementia. In other cases, while there may be a strong suspicion, regular review will be needed to monitor the course of these impairments and their relationship to mood symptoms. Although significant improvement in mood with antidepressant treatment can be associated with improvements in cognition, this is not necessarily the case and when it does occur it should not rule out an underlying dementing illness. Even in those with unipolar disorder, cognitive impairments are now known to persist after depression itself remits.

Depression is a risk factor for dementia

Meta-analyses of depression studies have shown that depression is associated with a doubling of the risk for subsequent dementia even when it occurs many years before the onset of the dementia; that is depression, even in middle age, is an independent risk factor for dementia (Ownby et al., 2006). It is not clear, however, whether this increased risk applies equally to all types of dementia. For example, a nine-year follow-up study finding depression to be a risk factor for dementia reported that depression increased the risk of VaD by threefold but did not increase the risk of AD (Kohler et al., 2011).

Cognitive impairment (and 'pseudodementia') as a feature of depression

It is established that in adults of all ages without dementia who develop depression and who do not progress to dementia over the following few years, cognitive impairment is a common feature and arguably is part of the core of depressive illness (Austin et al., 2001). Various terms have been applied to the clinical complex of cognitive impairment occurring in the context of depression, of which 'pseudodementia' is the most well known. 'Pseudodementia' is poorly defined, which may be related to its widespread use. It may mean simply someone with depression who complains of 'memory problems' and is said to be forgetful; or when someone with depression scores in the mid-20s on the MMSE; or when someone with depression has clinically significant impairment on testing with associated functional impairments (i.e. they appear to have a true dementia associated with the depression); or it may be used when detailed neurocognitive testing reveals deficits which are greater than expected for age. The term pseudodementia is therefore best avoided because of its vagueness.

Clinically it is important to examine not just a score on a cognitive test but the pattern of the deficits. Neurocognitive impairment in depression has a characteristic pattern of inattention, executive and amnesic deficits but aphasia, agraphia, apraxia, and acalculia/alexia all suggest the presence of a dementia (Butters et al., 2004; O'Brien et al., 2004). Consistent with the view that neurocognitive impairment is a core feature of depression it persists after remission of clinical symptoms (Bhalla et al., 2006) for up to at least four years (Kohler et al., 2010a). Although in some cases this impairment may only be detectable by detailed

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neuropsychological examination, in other cases it is apparent at interview and fitting with this longstanding clinical observation of cognitive impairments in older people with depression a large proportion (40% (O'Brien et al., 2004) and 54% (Lee et al., 2007)) of those with late-life depression were found to meet criteria for mild cognitive impairment (MCI).

This pattern (poorer information processing, amnesia, and executive dysfunction) is very similar to that of ageing (Austin et al., 1999) and thus as expected age explains a larger portion of these deficits (Kohler et al., 2010a; Sheline et al., 2006). This raises the question as to whether the greater severity of cognitive impairment characteristic of late-life depression compared with depression in younger adults is simply due to ageing effects? This does not seem to be the case. Studies that have carefully excluded people with early dementia and compared older and younger adults with depression matched for depression severity have found that, even after controlling for the age-related increase in impairment, adults with late-life depression have more severe impairments in memory and executive functions (Lockwood et al., 2002, Thomas et al., 2009).

Thus, people with late-life depression who are not developing dementia have more severe neurocognitive impairments due to factors associated with depression in older age, in addition to the well-recognized age-related increases. What might these depression related factors be? Some studies have related cognitive impairment to dysfunction in the hypothalamic pituitary adrenal axis (HPA axis) and associated hypercortisolaemia (O'Hara et al., 2007) and possession of the short allele of the serotonin transporter has also been linked to cognitive deficits (Hickie et al., 2007; O'Hara et al., 2007). The most robust and consistent relationship is between white matter hyperintensities (WMH) and these deficits (Thomas and O'Brien, 2008). Most studies have been cross-sectional but WMH at baseline also are the best predictor of persistence of these impairments over the following years (Kohler et al., 2010b). Apart from WMH, detailed studies examining correlates between regional and structural brain changes and cognition have not been reported, nor have correlations between functional brain changes in the frontal lobe and impaired cognition been shown.

Differential diagnosis of depression, mild cognitive impairment, and dementia

A clinical conundrum is differentiating from among patients with 'mixed depression and dementia' those who have major depression with associated cognitive impairment (and are not in prodromal dementia) from those who have an early dementia and prominent depressive symptoms (or a true double diagnosis of depression and dementia).

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Research studies involve a quality and depth of cognitive testing beyond what can usually be carried out in clinical practice. As above, such studies are able to identify both prominent impairments, which might be identified in the clinic, and more subtle abnormalities. In clinical practice impaired information processing may manifest itself as poor concentration, and memory and executive problems may be identified by routine tests in clinic, but these typically appear much milder than is found in people with (even early) dementia. Where such deficits are more marked, then a prodromal dementia should be carefully considered. In such cases, special attention should be paid to identifying the timing of the onset of mood symptoms in relation to the cognitive impairments and to assessing the impact on everyday living, where more marked problems are typical of those with early dementia. However, the pattern of cognitive deficits is often more helpful in distinguishing depression related impairments from those occurring in an early and prodromal dementia. Problems with praxis and language (dyspraxias and dysphasias) are characteristic of early dementia and rarely detectable in 'pure' depression and thus the presence of either and especially both strongly suggests an underlying dementia is present and this should then be investigated accordingly with neuroimaging and more detailed neurocognitive assessment.

Aetiology

The reason why some older people develop depression and others do not is not understood. Most of the risk (and protective) factors considered below affect far more people than those who develop depression (see Box 39.1 and Box 39.2). For this reason, the genesis of a depressive disorder is widely considered to be multifactorial, involving a complex and poorly understood interaction between vulnerability factors, which predispose people to developing depression, and precipitating factors which initiate a depressive episode; in many cases these precipitating factors can act to perpetuate the episode too. Vulnerability factors are often permanent (e.g. sex and other genetic risk) or at least difficult to alter (e.g. social isolation, disability, and white matter ischaemia), becoming factors that persist beyond a specific episode.

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Box 39.1 Risk factors for depression

Lack of intimacy	Female
Poor social support	Family history of depression
Being a carer	Physical illness
Bereavement	Brain disease

Box 39.2 Protective factors for depression

Self-efficacy
Mastery of environment
Wisdom
Religious practice

The evidence supporting different aetiological factors in late-life depression is pragmatically divided into two categories. The first groups together social risk factors, personality factors, and life events because these factors are generally recognized to be inter-related and because research in these areas has tended to investigate subjects with milder, more broadly defined levels of depression. The second group of biological factors also interact with each other and research into these risk factors has generally focused on more severe major depression, usually drawn from secondary care samples. This division is not intended to suggest there are two different types of depression or that factors in one category are not relevant to those in the other.

Social factors, personality, and life events

There has been little research into the relationship of personality to the risk of developing depression in old age and evidence points to (different) personality traits as being both risk factors (Box 39.1) and protective factors (Box 39.2). Historically, experts have claimed older people with depression have had stronger personalities than younger adults growing old with depression, indicating these were not risk factors in the development of their depression (Roth, 1955) or that older people with less severe community-type depression had more abnormal personality traits than older people with major depression (Post, 1972). Such views

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are close to a more widespread opinion that more severe depression (major depression) is more biological in its development, while less severe forms of depression are more influenced by personality and psychosocial risk factors. A difficulty in interpreting the limited data in this field is that the direction of causality between these risk factors and depression is unclear as most studies have been cross-sectional and thus unable to determine whether a depression preceded or followed the event.

Lifelong lack of capacity for intimacy has been reported as a risk factor for late-life depression in both sexes (Murphy, 1982), in men only (Emmerson et al., 1989), or women only (Pakhala, 1990). While 'capacity for intimacy' is not itself a personality variable it is related to personality but also to one's social situation, which in turn is related to personality making assessment of this difficult. Such assessments are also confounded by current mood state. Another study failed to identify any relationship with intimacy but found depression associated with a lack of general social contact (Henderson et al., 1986) and the perception that depression in older people is frequently related to loneliness and social isolation is common (Blazer and Hybels, 2005). More positively self-efficacy and mastery over one's environment are reported to be protective factors for late-life depression (Blazer and Hybels, 2005). Along the same lines is evidence that psychological resilience (an ability to properly interpret and understand events and persevere through them) and adaptive coping styles reduce the risk of depression after adverse life events (Arean and Reynolds, 2005). Wisdom in older people—which, like capacity for intimacy and psychological resilience, is an ill-defined but generally understood concept—has also been reported to be associated with greater life satisfaction (Reichstadt et al., 2010) and to be protective against depression (Blazer and Hybels, 2005). Such personality factors are not only difficult to define and influenced by one's social setting, upbringing, and experience, but in terms of the development of depression they interact with life events. That is, different people handle the same life events differently and thus not everyone who loses a loved one or suffers other adverse life events develops depression. And although research generally examines negative life events, people experience positive ones, e.g. marriages of children or births of grandchildren, which can be mood elevating.

The role of social isolation and lack of social support in influencing the development of depression has been mentioned and this is a risk factor in African (Gureje et al., 2011) and Japanese (Kaji et al., 2010) as well as western societies. Poverty and being a victim of crime, which are inter-related, have also been reported to be risk factors (Arean and Reynolds, 2005). Being a carer of someone, an increasingly common experience for older people, is another important risk factor for depression, with one study reporting that a quarter of carers of people with dementia were depressed (Ballard et al., 1996b). Religious practice has been reported to

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protect against depression in older adults in both western (Braam et al., 2001) and eastern cultures (Bosworth et al., 2003).

Life events have been associated with the development of depression in older people, although it is important to remember that the impact of life-events on mood is mediated by cognitive coping style (Meyer et al., 2010). One study reported that 48% of depressed older people had had at least one severe life event in the previous year compared with 23% of their non-depressed peers (Murphy, 1982). These events included death of a loved one, life-threatening illness to somebody close, major financial problems, and having suddenly to give up one's home. Although broadly similar to findings in younger adults, an important difference was the role of physical illness, either a chronic disabling one or a severe and recent illness. The former relationship is supported by other findings of a relationship between disability and handicap and depression. A study in London of 654 people over 65 found broadly defined depression associated with living alone, low income, and low social support, but that the strongest association was with disablement, particularly handicap (Prince et al., 1997a). Life events (most strongly bereavement, personal illness, and theft), especially in the preceding six months, also had associations with depression (Prince et al., 1997b). Handicap may simply be a summary factor for all the social disadvantage and chronic difficulties associated with depression, but a prospective analysis of this cohort found disablement, especially handicap, to be strongly predictive of incident depression (Prince et al., 1997b). The problem is how to interpret this broadly defined construct since it appears to include contributions from all the physical illness and psychosocial factors which have been shown to be risk factors for depression. Life events in childhood, as well as recent life events, have been associated with an increased risk of depression, but the former did not increase the risk of the latter producing depression; that is, childhood events did not confer vulnerability for late-life depression (Comijs et al., 2007).

Bereavement is reported as a frequent precipitant of depression in older people. However, the relationship of bereavement to depression is complex and appears to be mediated by social context and personality factors (Pai and Carr, 2010). First, there is the need to distinguish symptoms of normal grief from similar symptoms of depression. In the first month of bereavement, most people experience low mood, anorexia, insomnia, episodes of weeping, fatigue, loss of interest, and guilt. Such symptoms tend not to be as persistent or severe as in depression and when guilt is present the focus is on perceived failures towards the deceased, and generalized pessimism and suicidal thinking are rare. These symptoms gradually wane as grief is dealt with and by about a year are largely gone. However, in older people who have lost a spouse after many years of marriage, it is understandable that some grief symptoms continue for a long time episodically following the loss, e.g. occasional weeping when reminded of the loved one. Such symptoms are likely to worsen at key dates, e.g. the wedding anniversary. Importantly, normally

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the bereaved person is able to return to a pre-bereavement level of functioning and while such low-level grief symptoms may return from time to time, they are not continuous and the persistence of symptoms, especially when they affect day-to-day functioning, suggests a depression has developed. In addition to such a failure to resolve grief symptoms, other markers of concern are generalized guilt, severe feelings of worthlessness, wishing one were dead, suicidal thinking, psychomotor changes, and 'mummification' (where grief is perpetuated by a failure to adapt one's lifestyle appropriately to the loss). In interpreting the impact of bereavement, it is important to remember that grief is a highly personal and individual experience. Thus, loss of a spouse may be a major blow to one man who had enjoyed a warm and supportive relationship with his wife, but a relief to another who had endured many years of tension, arguments, and violence. Furthermore, different people have differing levels of social support to help buffer the impact of grief and different personality traits, which, as mentioned, may either confer resistance to developing depression or vulnerability. Thus, a quarter of those experiencing a major adverse event did so without developing depression. It is clear not all adverse events are followed by depression and not all depressive episodes are preceded by adverse life events. As discussed, the concern regarding the removal in DSM-5 of the bereavement criterion is that its removal may *discourage* the careful analysis of the relationship between adverse events and depression, whereas good clinical practice involves such a careful evaluation.

Medical and biological factors

Depression in all ages occurs more frequently in women (Cole and Dendukuri, 2003) and a previous history of either major depression or dysthymia increases the risk of developing another depressive episode in old age (Cole and Dendukuri, 2003). It is often said that genetic risk for depression declines with age, but it is important to clarify that if present this decreased risk applies to LOD. Studies comparing people with a first episode of depression in old age with those whose first episode was earlier in life have consistently reported that the former have fewer relatives with depression, e.g. (Baldwin and Tomenson, 1995; Brodaty et al., 1997; Brodaty et al., 1991; Hopkinson, 1964) and this has been confirmed by systematic review (Levinson, 2006). In contrast, a large Danish twin study found no change in the heritability of depression with increasing age (Johnson et al., 2002) and a Genome Wide Association Study (GWAS) of over 3,500 subjects also found no change in heritability of depression with increasing age (Demirkan et al., 2011). As has long been reported, this study confirmed that heritability in depression at all ages appears to be due to multiple genetic loci of small effect rather than it being related to a few genes of large effect (Flint and Kendler, 2014). Although candidate genes related to monoamine systems have been linked to major depression in some studies and other genetic loci implicated, e.g. polymorphism of the serotonin transporter promoter

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region (5-HTTLPR), there remains no convincing evidence for a significant effect on depression from any single gene (Levinson, 2006).

Several major diseases have been associated with high rates of depression. As noted, neurological disorders, especially those causing dementia, are strongly associated with high rates of depression. But vascular diseases and risk factors have an especially strong relationship with depression. Ischaemic heart disease (IHD) is associated with a two- to threefold increase in depression and stroke disease with a similar increased risk, and it has long been clear that the relationship between each of these and depression is bidirectional, with depression being an independent risk factor for IHD and stroke as well as these predicting increases in subsequent prevalence rates of depression (Valkanova and Ebmeier, 2013). It is also now clear that the same is true of diabetes (Rotella and Mannucci, 2013), with depression being a stronger risk factor for the development of diabetes than diabetes is for depression (Mezuk et al., 2008), and also hypertension, with depression increasing the risk of high blood pressure by about 40% (Meng et al., 2012).

The cause of the relationship of these to depression varies and involves several components. In some cases (especially the neurological and vascular disorders) there is good evidence for a biological relationship (see *Neurobiology of late-life depression*). In others pain and discomfort related to physical ill health, including to hip fracture and chronic painful conditions such as rheumatoid arthritis, appears to mediate depression via psychological pathways, which are thought to be bidirectional (Lin et al., 2003). Another aspect of the complex relationship between depression and physical ill health is that involving the handicap induced by the illness. The physical impairments of a significant illness create disability, which in turn places the sick person at a societal disadvantage, which constitutes their handicap (Prince et al., 1998). Thus, an impairment induced by an illness will produce differing degrees of handicap in different people because of their differing social situations. For example, one person with chronic obstructive pulmonary disease living alone may become highly socially isolated and depressed due to this loss of personal contact, while another person with the same condition living with a spouse is able to get out and about and enjoy company at home. Understanding the relationship of physical illness to depression involves careful consideration for each individual of the interplay between these biological, psychological, and social elements.

The possible role of drugs, for older people mainly medication and alcohol, should also be considered. Alcohol may lower mood and high alcohol intake may lead to depression or aggravate it, but often excess alcohol consumption is a consequence of a depression, with it being consumed to try to minimize the painful depression-related feelings. Assessment of depression should always include a sensitive consideration of the role of alcohol. Some reports have claimed different types of prescribed medication are associated with depression. For example, an epidemiological study from the Netherlands estimated the Population

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Attributable Risk percentage (PAR%, the proportion of depression in the population attributed to a drug) for a range of common treatments and found the PAR% for β -blockers was 2.5%, for calcium antagonists 5%, and for benzodiazepines 15.42% (Dhondt et al., 2002). However, such data is very difficult to interpret because people are taking medication for pre-existing diseases, which are themselves related to depression, and detailed assessments trying to tease out the contribution due to drugs themselves have not clearly supported a role for them in causing depression. For example, after reports that calcium channel blockers were associated with depression, a review of these demonstrated this was not the case (Dunn et al., 1999) and secondary analyses of studies in hypertension have reported possible benefits of calcium channel blockers on mood (Ried et al., 2005). While it is prudent to reflect on the possible role of medication when depression appears to start after a treatment is commenced, it would be rash to consider switching medication unless a convincing relationship is present given the precarious nature of the current evidence base. Since most older people are on multiple medications, it is likely to be difficult to decide which, if any, medication may be worth stopping or changing.

Neurobiology of late-life depression

The most widely known neurobiological abnormalities are those which involve the monoaminergic neurotransmitters serotonin and noradrenaline, because all conventional antidepressants target these two neurochemicals. However, research on monoamines is only a small part of the much wider evidence identifying neurobiological abnormalities in older people with depression, although most of the evidence comes from studies of major depression.

Neuroanatomy

Neuroimaging research in psychiatry has been central to the recognition that several neurally linked key brain areas underpin the symptomatology of depression and much of this research has focused on late-life depression. Studies in primates initially identified five frontal-subcortical circuits (FSC) and three of these, involving the dorsolateral prefrontal cortex (DLPFC)-head of caudate nucleus (DLPFC circuit), the anterior cingulate cortex (ACC)-nucleus accumbens (ACC circuit), and the orbitofrontal cortex (OFC)-head of caudate nucleus (OFC circuit) have been implicated in the regulation of mood (Lichter and Cummings, 2001). Evidence implicates dysfunction in these circuits in the onset and outcome of late-life depression (Alexopoulos, 2005), with changes most pronounced in late onset cases (Lloyd et al., 2004).

Structural imaging studies have shown that frontal lobe volume is reduced in depression (Sexton et al., 2013). Structural studies have identified specific areas of the prefrontal cortex as reduced in volume and functional imaging has confirmed these areas have reduced activity and/or blood flow in depression. Thus the ACC is smaller (Drevets et al., 1997)

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and has reduced blood flow (Drevets et al., 1997; Mayberg et al., 1997; Mayberg et al., 1999). The DLPFC is smaller (Chang et al., 2011) and has reduced blood flow (Baxter et al., 1989; Bench et al., 1992) and the OFC is smaller (Ballmaier et al., 2004; Bremner et al., 2002). Subcortically, decreased grey matter volumes in limbic and striatal structures have also been described in older depressed subjects in amygdala, thalamus (Andreescu et al., 2008), and hippocampus (Andreescu et al., 2008; O'Brien et al., 2004; Bell-McGinty et al., 2002; Steffens et al., 2011), as well as caudate (Butters et al., 2009; Krishnan et al., 1992; Parashos et al., 1998) and putamen (Andreescu et al., 2008).

The role of the FSC in the development of late-life depression is further supported by other areas of research. Thus ischaemic WMH are especially prominent in the frontal lobes and basal ganglia (Herrmann et al., 2008) and diffusion tensor imaging studies have reported white matter abnormalities in these same frontal areas (Wise et al., 2016). Neuropathological abnormalities have also been identified in these same brain areas (discussed in more detail later) (Khundakar and Thomas, 2009). As mentioned, studies of neurocognitive impairment in late-life depression have also shown a pattern (impaired information processing, memory, and executive function) consistent with this neuroanatomy and direct evidence of a relationship between the anatomical location of WMH and this neurocognitive impairment has been reported (Sheline et al., 2008).

These neurobiological investigations in late-life depression implicating the FSC have not focussed on the monoaminergic nuclei in the brainstem. The raphe nuclei (serotonin) and locus coeruleus (noradrenaline) in the brainstem are the other key brain areas forming the neuroanatomical substrates for depression.

Neurochemistry

The neurotransmitters relevant to depression can be conceived of as having executive and modulatory components. The former are the main neurotransmitters of the major projection neurones in the FSC, glutamate and gamma-amino butyric acid (GABA), and some evidence implicates abnormalities in these in depression (Sanacora and Saricicek, 2007; Zarate et al., 2010). The modulatory neurotransmitters are the monoamines (serotonin, noradrenaline, and also dopamine) projecting from their brainstem nuclei to widespread parts of the cortex, having dense input to the FSC areas. Abnormalities in serotonergic and noradrenergic neurotransmission are undoubtedly present in late-life depression, and this is most clearly supported by the proven efficacy of antidepressants which all target these transmitter systems (see Management of depression). Dopaminergic changes also may be present (Nestler and Carlezon, 2006) and may be especially relevant where apathy is present, reflecting loss of initiative and drive subsequent to loss of dopaminergic function; this is often the case in 'vascular depression' (discussed later). Although impairments in monoaminergic

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neurotransmission are present in late-life depression it is not clear there are any age-associated changes in these neurochemicals that might make older people more or less vulnerable to depression (Veith and Raskind, 1988). And the failure of a significant proportion of older depressed people to respond to the conventional monoamine-based antidepressants indicates not only that other transmitters may also need to be targeted, e.g. GABA and dopamine, but that other pathophysiological processes are likely to be important, including those affecting vascular, immune, and neuroendocrine systems.

Neuroendocrine

Dysfunction in the HPA axis is recognized to occur at all ages in depression and is associated with hypercortisolaemia, non-suppression on the dexamethasone suppression test, and a loss of the characteristic circadian rhythm of the HPA axis (Stetler and Miller, 2011). In addition, ageing itself is associated with a similar pattern of changes (Alexopoulos et al., 1984) so that HPA axis dysfunction is more marked in late-life depression (O'Brien et al., 1993).

Animal studies indicate that prolonged exposure to glucocorticoids may reduce dendritic density and increase neuronal death, and since the hippocampus has the highest concentration of glucocorticoid and mineralocorticoid steroid receptors in the brain, it may be especially vulnerable to such toxicity. High cortisol levels have also been reported to lower brain derived neurotrophic factor (BDNF) in the hippocampus, with antidepressants reversing this change (Sen et al., 2008). As mentioned, hippocampal atrophy has been frequently reported in depression in older people and amnesia is a prominent problem on detailed cognitive assessment. Thus, HPA axis dysfunction may help explain the prominence of amnesic deficits in late-life depression. Although one study reported a relationship between potential exposure to high levels of cortisol and hippocampal atrophy (Sheline et al., 1996), other studies have not replicated this (O'Brien et al., 2004), nor is it apparent that amnesic deficits are related to HPA axis dysfunction and so it is not clear how important this mechanism is in late-life depression.

Immune and inflammatory

The suggestion of a relationship between depression and the immune system dates back to at least 200 AD when Galen claimed that melancholic women were more susceptible to breast cancer due to immune deficiency. Research during the last two decades has made it clear that the nervous, endocrine, and immune systems are so closely connected that it is suggested that they should be regarded as a single network, and their intimate relationship has led to the development of the new discipline of psychoneuroimmunology. Initially it was thought that psychological stress and depression compromised immune function (Irwin et al., 1990), but studies failed to replicate initial findings and more recent studies indicate depression is associated with immune activation,

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including increased peripheral blood mononuclear cells (such as neutrophils, monocytes, and activated T-lymphocytes), increased secretion of prostaglandin E2, and the presence of a moderate acute phase reaction (with increased haptoglobin, C-reactive protein and α 1-antitrypsin) (Dowlati et al., 2010).

Linked to this immune response is evidence of increases in pro-inflammatory cytokines and reductions in anti-inflammatory cytokines in depression (Dowlati et al., 2010). Cytokines are proteins (such as interleukins, tumour necrosis factor, and interferons) secreted by a variety of cells, including glial cells in the CNS, which play a key role in mediating immune and inflammatory responses. Brain cytokines have a broad range of immunological, neurochemical, neuroendocrine, and behavioural effects (Rothwell and Luheshi, 2000) and their release during illness is associated with so-called 'sickness behaviour' including symptoms such as fatigue, anorexia, depressed mood, hopelessness, anhedonia, and poor concentration. Most studies in depression demonstrating increases in cytokines have been on younger adults but in late-life depression, similar changes have been observed. IL-1 β , IL-6, and TNF- α have all been reported to be raised in both depression and dysthymia in both community (Dentino et al., 1999; Penninx et al., 2003) and hospital-based studies (Thomas et al., 2005) and there appears to be a dose-related effect (Dentino et al., 1999; Penninx et al., 2003; Thomas et al., 2005).

Neuropathology

The neuroimaging evidence identifying structural and functional changes in FSC in depression led to post-mortem neuropathological investigations seeking to identify the cellular correlates of these abnormalities. These studies utilized unbiased stereological methods, to estimate changes in the size of neurons and density of neurons and glia (Khundakar and Thomas, 2009). In younger adults such studies have consistently reported a reduction in glial density in major depression in the ACC (Cotter et al., 2001; Ongur et al., 1998), DLPFC (Rajkowska et al., 1999), and OFC (Rajkowska et al., 1999), but no differences in neuronal density or number. In contrast studies of late-life MDD have reported no evidence of reduced glial density in cortical areas (Khundakar and Thomas, 2009). Overall the findings are suggestive, but not conclusive, that subtle neuronal abnormalities, reductions in pyramidal cell volume, may be present in key areas of the FSC in late-life depression (Khundakar and Thomas, 2009). The prefrontal pyramidal neurones are mainly glutamatergic, and as well as projecting to other cortical areas, also project to the striatum and it may be that ischaemic WMH affect the axons of these neurons inducing these subtle changes.

Other neuropathological investigations have directly examined WMH to assess their pathology. In a study comparing 20 people with late-life depression and 20 age-matched controls, deep WMH were identified on post-mortem imaging and then examined microscopically. While some

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lesions in controls were due to myelin pallor that was not ischaemic, all WMH in depression were ischaemic and the difference from controls was most marked in the DLPFC (Thomas et al., 2002b). This indicates that not only are deep WMH increased in late-life depression but that such deep WMH are due to cerebrovascular disease and that such disease is more frequent in late-life depression. In contrast to these findings in deep WMH, examination of periventricular WMH found most, whether in control or depressed subjects, were not ischaemic but due usually to disruption of the ependymal lining of the ventricles (Thomas et al., 2003). These findings support earlier work on the relationship of vascular risk factors (VRFs) to WMH, which indicates that while deep WMH are strongly related to VRFs and are due to brain ischaemia, PVH are not. Other studies identified an increase in cell adhesion molecules, markers of an ischaemia induced inflammatory reaction, in the DLPFC in late-life depression in both the grey and white matter, suggesting ischaemic brain disease in late-life major depression extends beyond WMH into other white matter and grey matter (Thomas et al., 2002a; Thomas et al., 2000).

Post-mortem studies have also identified evidence of an increase in atheromatous disease in depression in older people (Thomas et al., 2001), which was present even though subjects were matched for vascular risk factors and this was supported by a clinical study also identifying an increase in atheroma in late-life depression (Tiemeier et al., 2004). Although such studies provide evidence of an increase in vascular and cerebrovascular disease there is no evidence of an increase in neurodegenerative disease in late-life depression in subjects who were cognitively intact at death in either the cortex (O'Brien et al., 2001; Tsopelas et al., 2011) or brainstem (Hendricksen et al., 2004; Syed et al., 2005). These autopsy findings are supported by PET amyloid imaging studies reporting no differences in amyloid deposition in late-life depression compared with age-matched healthy controls, e.g. (De Winter et al., 2017).

White matter hyperintensities

Cerebral white matter lesions, usually referred to as WMH, identified on magnetic resonance imaging (MRI) are frequently reported in older people (Jeerakathil et al., 2004) but many studies have demonstrated they are increased in depression in older people (Herrmann et al., 2008). Box 39.3 summarizes their relationship to depression in older people. Although most of the research has been on major depression from hospital-derived samples, several community-based studies of depression in older people have also reported increases in WMH (de Groot et al., 2000; Steffens et al., 1999). WMH are more common in LOD than EOD (Herrmann et al., 2008; Teodorczuk et al., 2007). These lesions have frequently been associated with hypertension (Dufouil et al., 2001; Jeerakathil et al., 2004) and other vascular risk factors, such as carotid atherosclerosis (Pico et al., 2002) and smoking (Jeerakathil et al., 2004). WMH have been associated with VRFs in depression specifically (Smith et al., 2010; O'Brien et al., 1996) and additionally in late-life depression

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WMH have been associated with orthostatic hypotension and drops in systolic blood pressure (Richardson et al., 2009; Vasudev et al., 2011). They have therefore been widely regarded as due to cerebrovascular disease and this has been demonstrated to usually but not always be the case in post-mortem studies (Fernando et al., 2006; Thomas et al., 2003; Thomas et al., 2002b) and in late-life major depression WMH are more frequently due to cerebral ischaemia than in age matched controls (Thomas et al., 2002b). WMH are especially increased in the frontal lobes and basal ganglia in older people with depression (Herrmann et al., 2008), and have been related to the neurocognitive impairments characteristic of depression (Sheline et al., 2008).

Box 39.3 MRI white matter hyperintensities and depression

- Increased in volume
- Increase in volume over time
- More prevalent in frontal-subcortical areas
- Associated with vascular risk factors
- Due to ischaemic brain disease
- Predict future depressive symptoms and episodes
- Associated with poorer remission rates
- Predict chronic cognitive impairment

Prospective studies have reported WMH to increase in volume over time in older people with depression (Taylor et al., 2003) and that these lesions have a bidirectional relationship with late-life depression. Baseline severity of WMH predicts the development (Godin et al., 2008) and worsening of depression (Teodorczuk et al., 2010, Teodorczuk et al., 2007) but depression also predicts the worsening of WMH (Godin et al., 2008). Although the impact of antidepressants on the development and progression of WMH has not been examined, it has been reported that antihypertensive treatment reduces the progression of WMH (Dufouil et al., 2005; Firbank et al., 2007). Since it is clear WMH have an adverse impact on treatment response and longer-term outcomes (see Management) then the amelioration of these lesions by medication raises the hope that their likely role in the development and maintenance of depression could be attenuated.

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‘Vascular depression’

Evidence clearly demonstrates depression has a bidirectional relationship with vascular disease (Thomas et al., 2004). Prospective studies of vascular diseases have reported that previous major depression or depressive symptoms predicts a two- to threefold increase in coronary heart disease, e.g. (Ford et al., 1998; Pratt et al., 1996) and stroke disease, e.g. (Jonas and Mussolino, 2000; Salaycik et al., 2007). The increase in WMH, which are ischaemic lesions, in late-life depression provides direct evidence for a role of cerebral ischaemia and this is further strengthened by reports from diffusion tensor imaging studies of increased diffusivity in late-life depression (Wise et al., 2016), which is a further indicator of the presence of white matter tract disruption due to cerebral ischaemia. This increased diffusivity occurs in areas without WMH, suggesting a more widespread impact of cerebrovascular disease than that identified by MRI WMH, and this is further supported by neuropathology reports of increased cell adhesion molecule expression in the DLPFC, showing vascular changes in frontal grey as well as white matter (Thomas et al., 2002a).

This evidence led to and provided support for the ‘vascular depression’ hypothesis (Alexopoulos, 1997, p. 118), which postulates that cerebral ischaemic damage to frontal-subcortical circuits predisposes to and/or perpetuates depression in older people. This concept has received criticism because delineation of a recognizable sub-group of ‘vascular depression’ has proven difficult (Baldwin, 2005). More importantly several community studies of late-life depression have not identified an increase in clinically determined VRFs (Kim et al., 2004; Lyness et al., 1998; Lyness et al., 1999; Naarding et al., 2007), casting further doubt on the importance of specific VRFs in the genesis of late-life depression. It is important to note, however, that the same cohorts followed prospectively have reported an association of depression with some VRFs (Kim et al., 2006; Lyness et al., 2000) and that the increases in WMH occur independently of the association with VRFs (Herrmann et al., 2008). This has been directly demonstrated in a large study matching depressed and control groups for VRFs (Sheline et al., 2008). The explanation for these discrepant findings probably reflects the insensitivity of (peripherally measured) conventional VRFs for actual ischaemic disease in the brain and the differences in samples, with the MRI and pathology studies assessing major depression in secondary care patients while the community studies sample milder cases of depression. The ‘vascular depression’ model postulates that cerebrovascular disease is an important aetiological factor in late-life depression and likely to be an important one in a proportion of such people, but does not propose a unifying mechanism involving vascular disease for *all* late-life depression. Estimates of the proportion of people with late-life major depression where vascular disease is important indicate this is likely to be the case in about 50% (Sneed et al., 2008a) and this delineation was based on utilizing evidence of significant WMH on MRI, rather than VRFs. Two

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intervention studies using the calcium channel blocker nimodipine have also provided encouraging results (Taragano et al., 2001, Taragano et al., 2005) suggesting the 'vascular depression' model may provide a way of developing new treatment approaches in late-life depression.

Management of Depression

The clinical management of depression requires a thorough assessment and diagnosis, since diagnosis in older people is frequently difficult because of confounding cognitive impairments and physical illnesses and because one neglected reason for non-response to treatment and treatment resistance is misdiagnosis. Assessment should aim to generate an understanding of the individual impact of the current depressive episode on the patient and his everyday life, and not merely be a process of identifying and counting depressive symptoms, since the number of symptoms is not a good guide to the severity of depression. Assessing the degree of functional impairment or disability related to the depression is key to developing a good management strategy. This allows the potential benefits and risks of treatment to be carefully weighed. This approach was proposed in the British Association of Psychopharmacology guidelines (Anderson et al., 2008) and has been adopted by NICE in its Guidelines for the Management of Depression (NICE, 2009). These both emphasize that identifying duration of symptoms and the disability associated with them is crucial to informing rational management and leads to a stepped care approach based on the combination of burden of symptoms, duration of illness, and depression-related functional impairment.

Assessment has been discussed in detail in Chapter 9 and earlier in this chapter and here a few brief points relevant to depression management are emphasized. A careful risk assessment, including sensitive questioning about suicidal thinking and previous acts, is an integral part of the assessment of depression. When depression is severe, suicidal thinking should be suspected and careful monitoring instituted even where such thinking is not volunteered. In such cases it is also important to probe for symptoms of psychosis, especially mood congruent delusions. A cognitive assessment should be carried out whenever there is suspicion of cognitive impairment; however, this need not always be the case and in those presenting with a 'pure' depression this may be unhelpful, and suggesting a dementia is suspected that might damage the therapeutic relationship. In those with a previous history of depression it is important to obtain details of treatments for these earlier episodes, whether they were successful or unsuccessful, as this can be very helpful in guiding treatment of the current episode because patients tend to respond, or not respond, to the same treatments.

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General principles of management

As when treating younger adults it is helpful to consider treatment as having three stages: an acute phase, a continuation phase, and a maintenance phase (Frank et al., 1991). The stepped care approach recommended by NICE and BAP applies to the acute phase, and ties in with an important finding in clinical trials of antidepressants: the more severe the depression, the stronger the evidence for efficacy and the greater the benefit from using this medication (Khan et al., 2002; Kirsch et al., 2008). This increased benefit comes both from antidepressants having a larger reduction in depression when depressive illness is more severe and from placebo having a smaller impact on depressive symptoms in the more severely ill (Khan et al., 2002). The conclusion from this is that a clinician needs to weigh up the severity of the depressive illness when considering whether to use antidepressants and how vigorously to treat. Thus, following the stepped care approach, those with few symptoms ('subthreshold') and little impact on everyday functioning should not be offered antidepressants, but instead be given supportive and low-intensity psychosocial interventions. In those with so-called mild major depression, better 'minor depression', a more intensive psychological treatment is indicated but antidepressants are unlikely to be of benefit. In such cases antidepressants should be reserved for when such interventions fail and disability is significant. Those with moderate or severe major depression are those most likely to benefit from antidepressants and medication is then indicated as first-line treatment, and combining medication with intensive psychological treatments is often appropriate. This leads back to the British Association of Psychopharmacology recommendations of its 'dimensional' approach to prescribing antidepressants (Cleare et al., 2015). Those with MDD and significant severity (taking into account both symptoms and the impact on everyday living) should be treated robustly. Similarly, when someone presents with a longer illness, say over three months, even though the severity is milder antidepressants are indicated because spontaneous recovery or improvement is less likely.

There are several goals in the management of depression, but aiming to achieve clinical remission, rather than simply symptom reduction, is vital because persistence of depressive symptoms ('residual depression') is strongly associated with high rates of relapse. During the acute phase of treatment, management of suicide risk and possibly self-neglect are important and treatment aims at more than symptom relief by trying to achieve a restoration of previous levels of everyday functioning. Once this is achieved, then the management focus moves to reducing the likelihood of future depressive episodes through continuation and maintenance treatment. Continuation treatment usually means continuing with whatever treatment got someone well for at least six months after remission. While in younger adults with a first episode treatment may then be withdrawn, it is argued below that for major depression in older adults, continuation should always be followed by maintenance; all late-

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life major depression (but not necessarily milder forms of depression) needs lifelong treatment.

Prescribing in late-life depression

There are several general topics that need consideration when prescribing antidepressant medication in older adults. With ageing there are pharmacokinetic changes which alter the bioavailability of drugs. These are considered in detail in Chapter 13 and so only key aspects are summarized here. There is reduction in hepatic metabolism, which reduces biotransformation and the impact of first pass metabolism allowing more active drug to enter the systemic circulation; volume of distribution is typically increased with ageing due to the relative increase in adipose tissue; and, most importantly, there is an age-related reduction in glomerular filtration rate. Together, these changes lead to higher plasma and brain levels of active drug per unit dose compared with younger adults and consequently the need for lower doses. However, there is much variability in these changes and clinicians are used to observing such variability. Some 75-year-olds are much 'younger' physically than others and such 'younger' older people are likely to need and to tolerate higher doses; it is prudent to remember this if someone is not responding to a typical dose for an older adult.

A related factor which affects dosing at all ages is genetic variability. Polymorphisms in key enzymes of the cytochrome P450 system, which metabolize psychotropic drugs, can lead to a wide range of plasma levels for the same drug dose. Of course, in regular practice the clinician does not know which polymorphisms a patient possesses but it is helpful to be aware they exist because, as with variability in age-related pharmacokinetic changes, inadequate response to a standard or even 'high' dose of antidepressant may be because a 'high metabolizer' is being undertreated.

Pharmacodynamic changes also occur with ageing and are probably due to age-related changes in dendritic and synaptic density and may explain why some older people are more prone to adverse effects, e.g. antipsychotic-induced tardive dyskinesia (Jeste, 2000), even at low drug levels. And pharmacodynamic changes may also explain the propensity of older people to develop disabling tremor even with low serum levels of lithium.

In a different category from these biological alterations is polypharmacy. This continues to be a major issue in older adults and, given the large and increasing numbers of effective available treatments for illnesses strongly associated with ageing (statins, angiotensin receptor blockers, proton pump inhibitors, etc), it seems impossible to avoid. Awareness that the likelihood of adverse drug-drug interactions and related problems is proportional to the number of prescribed drugs should encourage regular medication review, especially where new symptoms develop when a new drug is added (Chrischilles et al., 2009). The number of psychotropic

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drugs being prescribed has increased significantly, making this an increasing problem (Mojtabai and Olfson, 2010). For example, the prescribing of antidepressants in nursing homes in the US more than doubled from 21.9% to 47.5% over the last ten years; interestingly, increased involvement by nursing staff was associated with an increase in antidepressant prescribing whereas more visits by physicians was associated with lower prescribing, perhaps due to a better understanding of depression and benefits from antidepressants in the latter group (Hanlon et al., 2010). Levels of polypharmacy remain very high. In India, a study of two teaching hospitals reported that over 90% of those over 60 were prescribed five or more medications and 45% were receiving ten or more (Harugeri et al., 2010). A survey of over 13,000 residents of nursing homes in the US found over 40% were being prescribed nine or more drugs (Dwyer et al., 2010).

Polypharmacy also raises the likelihood of clinically important additive side-effects, whereby common side effects may be tolerated from one medication but not when several are used together (Carnahan et al., 2006). For example, when prescribing a serotonin reuptake inhibitor (SSRI) it is important to check for other medication that can also cause gastric erosions and bleeding, especially because treatments such as aspirin, donepezil, NSAIDs, and steroids with such properties are commonly prescribed in older people. If after review it is concluded all such treatments are needed, then it will be necessary to also prescribe something such as a proton pump inhibitor for gastroprotection.

Finally, consideration should be given to frailty and reduction in homeostatic reserve. These are two related, but poorly defined and yet widely used, terms that point to the disproportionate impact side-effects can have on older people. Frailty means older people are less robust and so, for example, anticholinergic effects from paroxetine (especially if combined with other medication with anticholinergic effects, such as valproate, carbamazepine, or olanzapine) which may pass unnoticed in a healthy younger adult, may induce delirium in an older adult with depression.

Acute phase drug treatment of late-life major depression

The great majority of pharmacological studies of antidepressants have been conducted in people diagnosed as having major depressive disorder. It is important to remember this because it is not clear the abundant evidence for efficacy of antidepressants in this group can be extrapolated to the other types of depression occurring in older people. This is, of course, not an issue unique to late-life depression. In its guidelines for the drug treatment of depression, the British Association of Psychopharmacology recommends a 'dimensional' approach to prescribing antidepressants for depression (Cleare et al., 2015). This encourages clinicians to see the diagnosis of depression as a starting point, but not one that itself indicates that an antidepressant should be prescribed. Essentially the same approach is used by NICE in their

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clinical guidelines on depression management (NICE, 2009). This means combining evidence of depression severity with the duration of the illness, rather than simply making a diagnosis of depression and prescribing if someone meets this diagnosis. Such a nuanced approach is perhaps especially important in older patients, where the risk/benefit ratio is less clear due to the increased propensity of older people to develop adverse drug effects.

Meta-analytic systematic reviews have reported clear benefits from the use of antidepressants in late-life major depression (Kok et al., 2012; Nelson et al., 2008; Wilson et al., 2009a) and similar response and remission rates across the different antidepressant classes (Kok et al., 2012). However, the reported trials have been far from unanimous in this verdict and it is important to consider reasons why findings are heterogeneous. Some of the earlier trials were less well designed, especially those of tricyclic antidepressants, and in particular were often underpowered (Wilson et al., 2009a). However, these older antidepressants are used infrequently nowadays and so here we provide closer examination of 'modern' compounds that are widely prescribed for older people.

Specific SSRIs have the largest evidence base and overall are clearly efficacious in MDD although some trials have been negative (Nelson et al., 2008). An important reason for this in one trial in the 'old-old' (all subjects were over 75) was very large variation in outcome between different trial sites, which created so much noise in the outcome data that the signal of sertraline efficacy could not be detected. This problem is probably widespread in clinical trials and likely had an impact on another negative trial of fluoxetine and escitalopram (Kasper et al., 2005), which utilized 73 sites. Another important factor precipitating negative outcomes is the presence of cognitive impairment. In a systematic review of randomized controlled trials (RCTs) of non-tricyclic antidepressants in late-life depression (Nelson et al., 2008) it is noteworthy that those studies reporting no favourable outcome of medication over placebo (including the agents escitalopram, citalopram, fluoxetine, and venlafaxine) included subjects with a significant amount of cognitive impairment. This is likely to have contributed to the negative outcomes because neurocognitive impairment is associated with poorer outcomes generally. Indeed, a re-analysis of the data from one of these trials identified executive dysfunction as a predictor of poorer response to citalopram, with those without such impairments responding better than placebo (Sneed et al., 2010). It is worth adding the wider context including trials from younger adults. A network meta-analysis of 522 RCTs (Cipriani et al., 2018) including 116,477 subjects reported all antidepressants to be better than placebo and in head-to-head studies agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine performed better against other antidepressants, supporting the view that the negative trials of these agents in older people are probably due to other effects such as the

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presence of cognitive impairment. For newer non-SSRIs the evidence base is much smaller in late-life MDD but it seems reasonable to extrapolate this evidence from younger adults since the evidence for SSRIs and TCAs has been shown to reliably apply to older adults too.

There are now a large number of antidepressants to choose from, emanating from several distinct drug classes. In general terms, in making a choice one should consider tolerability, safety, side effects, drug interactions, and contraindications, and where relevant, previous history of antidepressant use. Achieving adherence to antidepressants is clearly important since merely prescribing an antidepressant will achieve nothing unless the patient is convinced of the need for taking it and does so. Older people frequently do not adhere to medication in general and this is likely to be especially the case for antidepressants. Hence, engagement of the patient during assessment, sensitive explanation of the diagnosis, and education about the benefits and side-effects of antidepressants is crucial. Antidepressants may still be confused with benzodiazepines and so thought to be 'addictive' and reassurance that this is not the case may be needed. Dose-related and common side-effects should be spelled out and encouragement given that persistence with the treatment is often associated with these waning. In the author's experience, patients often read and are upset by the much larger number of potential adverse effects listed on the drug insert in the box and it is helpful to explain that these consist largely of common everyday symptoms that are not necessarily related to the drug at all. Education about the speed of response to antidepressants should also be given, since people may expect the same kind of rapid response they have experienced with antibiotics and so become discouraged when this does not happen. At this stage a medication review is worthwhile because simplifying the medication regime is not only helpful for adherence to antidepressants, but also can improve adherence more generally and reduce the number of drugs being taken. Often treatments have been added in from time to time over years and, in liaison with the GP, some can often be stopped and a once daily or twice daily treatment regime can helpfully replace a more complex one.

Regarding the specific antidepressant to use, then guidelines indicate the first antidepressant should be an SSRI, unless the patient has a clear history of response to a drug from another class and/or failure to respond to or poor tolerability of an SSRI. This recommendation is supported by the above trials evidence in older adults and SSRIs are generally better tolerated than earlier antidepressants, especially tricyclic agents. SSRIs are generally free from significant interactions with other drugs, an important consideration in older adults who are usually on other medication, and are particularly appropriate where tiredness and excessive sleep is a problem because of their alerting properties. Mirtazapine, reported to be one of the four most efficacious antidepressants in depression (Cipriani et al., 2009), has a side-effect profile which is particularly suited for use in older people. Its main

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adverse effects are weight gain and sedation but in older people in whom sleep disturbance and weight loss are frequently problematic these can be helpful rather than problematic and the clinical experience of mirtazapine is that it is very well tolerated. It has the added advantage that its pharmacological profile complements that of SSRIs (and Selective serotonin and noradrenaline reuptake inhibitors (SNRIs)) as it has antagonism of 5-HT₃ and 5-HT₂ receptors which counteract the potential adverse effects of sexual dysfunction and nausea. For these reasons, mirtazapine has become a very widely prescribed antidepressant in late-life depression and is frequently used second line or in combination with an SSRI. SNRIs (duloxetine and venlafaxine) have similar side-effect profiles to SSRIs and may be especially helpful in those resistant to SSRIs where their dual action can prove helpful, and like SSRIs they can be combined well with mirtazapine.

An important caveat to the extrapolation of results from clinical trials in younger adults is that the data may only be valid in older adults who are healthy and cognitively intact, i.e. biologically like younger adults. Physical illness morbidity has been shown to predict poor response to antidepressants (Reynolds et al., 2006) and cerebral ischaemic white matter disease (demonstrated by the presence of WMHs on magnetic resonance imaging) is associated with a poorer response to antidepressants (Alexopoulos et al., 2002; Alexopoulos et al., 2008), poorer longer term outcome and increased relapse rates (Hickie et al., 1996; O'Brien et al., 1998), and persistent cognitive impairment up to four years (Kohler et al., 2010b). Since WMHs are associated with executive dysfunction it is not surprising that such impairment is itself associated with poorer response to antidepressants and increased relapse rates (Alexopoulos et al., 2000; Kalayam and Alexopoulos, 1999). Such findings are consistent with evidence indicating antidepressants are ineffective in depression in dementia (discussed later) and with the studies indicated earlier in which those enrolling subjects with (mild) cognitive impairments showed equivocal benefits for antidepressants. While the evidence may not be robust enough to indicate that antidepressants should not be used in such patients, it does suggest that more careful consideration is needed and that, if used, higher doses, augmentation, and combination strategies may be needed.

Acute phase psychological treatments of late-life depression

The quality of the evidence for using psychotherapies in late-life depression remains poor and the number of well-designed studies in this field continues to be disappointingly low. There are several particular problems in evaluating the evidence. Much of the evidence that is cited in support of psychotherapy for late-life depression is from non-randomized studies, and it has been shown that the design of such studies inflates the outcomes in favour of the intervention (Sneed et al., 2008b). Thus, for example, in one review (which did not include several important recent antidepressant studies included in the above meta-analysis (Nelson et al., 2008)) it was reported that the effect size in favour of psychotherapy in

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broadly defined late-life depression was 1.09 compared with only 0.69 for antidepressants (Pinquart et al., 2006). However, this was really an 'apples vs oranges' comparison, since randomized blinded antidepressant trials were compared with unblinded, non-randomized psychotherapy studies. Its findings also contrast with those of the Cochrane review (Wilson et al., 2009b) of psychotherapy in late-life depression that identified only 12 studies of sufficient quality to include, and even then had to include reports comparing psychotherapeutic interventions with waiting list controls. Most of the studies also included people with depression whose baseline HAM-D score only had to exceed 9 points (a low score, since <10 is often used as a definition of remission in drug studies). The largest and best designed study (Williams et al., 2000) found no benefit of problem solving therapy over placebo (though paroxetine did have significant benefits) and overall the review concluded the evidence for using psychotherapy in late-life depression is weak. It was also observed that the patients included in these studies did not appear to be representative of those usually attending health services, since most had been recruited through adverts, which appears consistent with the low score on the HAM-D for inclusion. Currently there is clearly a need for larger, better designed studies which enrol depressed subjects more typical of those seen in primary care and psychiatric services. It can also be argued that in the meantime the findings from studies in younger adults with depression can be extrapolated to older adults as with drug studies, though the same caveats apply about this probably only being valid for healthy, cognitively intact older adults.

When psychotherapy is needed there are added difficulties with availability and therapist experience. Availability of specific psychological interventions is still limited, especially in older adults, and identifying someone expert in the required therapy, e.g. cognitive behavioural therapy (CBT), can be especially difficult. When prescribing medication the treatment is the same regardless of the prescriber but in psychotherapy there is large variation in the experience and expertise of therapists and this has been reported to directly affect the efficacy of the intervention (Williams et al., 2000). Thus, even when psychotherapy is indicated it can be difficult to ensure a quality of therapy is provided comparable to that in the published literature.

An important issue not covered in the literature is anxiety management in the context of depression. So-called comorbid anxiety is common in late-life depression and frequently persists once (other) depression symptoms have resolved. Anxiety management, involving psychoeducation on anxiety symptoms and techniques such as controlled relaxation, can in such circumstances be helpful and delivered by nurses or occupational therapists from local services.

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Multifaceted interventions

In contrast to the disappointing quality and quantity of the evidence for using specific psychotherapies in late-life depression, there are an increasing number of studies examining a combination of psychotherapeutic and other interventions to provide structured packages of care. Various 'packages' have been investigated but almost all of these studies have provided encouraging findings. One study of home-based treatment for older people with depression, for example, compared PEARLS (combined problem solving therapy, increased physical activity, and increased socialization) with usual care and found a 50% depression symptom reduction was achieved by 43% of the PEARLS group, compared with 15% with usual care and remission rates were 36% and 12%, respectively (Ciechanowski et al., 2004). The largest study (involving 1,802 patients) of such an approach is the IMPACT study, which compared usual care with a care management package, with patients being able to select between antidepressants and problem-solving therapy (PST). At 12 months, 45% of intervention patients had achieved a 50% reduction in symptoms, compared to 19% in the usual care group (Unutzer et al., 2002). The PROSPECT study, using a collaborative intervention based in primary care, has reported improved remission rates in late-life major depression at 6, 12, and 24 months and reduced suicidal ideation (Alexopoulos et al., 2009). A similar but flexible approach was used in a study in Austria comparing home-based treatment by a multidisciplinary team with usual care and reporting significant improvements in depressive symptoms, quality of life, and overall function, and a reduction in admissions to hospital and nursing homes over one year (Klug et al., 2010). Similarly, the use of a dedicated depression care management approach in primary care led to markedly improved outcomes (effect size 0.8) compared with usual care (Chen et al., 2015).

These multifaceted interventions often include 'exercise therapy' of different kinds and the evidence for benefit from exercise in depression is similar to that for specific psychotherapies in that most of the studies in the literature are of poor quality and a systematic review found only 15 randomized studies, most of which were not blinded and had inadequate follow-up (Sjosten and Kivela, 2006). The review concluded that the evidence justifying exercise therapy is modest and its role is probably best within such a multifaceted approach. Overall these multifaceted studies have applied their interventions in outpatients (Sirey et al., 2005), community patients (Banerjee et al., 1996; Ciechanowski et al., 2004; Unutzer et al., 2002) and even in residential care (Llewellyn-Jones et al., 1999) and consistently reported benefits. These findings provide robust evidence for enhancing the quality of community-based care by applying such structured interventions in regular clinical practice, though unfortunately this is often difficult to achieve.

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ECT and other interventions

The other major treatment regularly used in clinical practice for late-life depression is electroconvulsive therapy (ECT). Its use is reserved for those who remain ill and disabled after other interventions have been tried and those with life-threatening illness (including high suicide risk). Concerns about using ECT in older people are often expressed, mainly about precipitating confusion and the alleged increased risks of other physical adverse effects, but the evidence strongly supports its use. Well-conducted studies (comparing real ECT with sham ECT, in which electrodes are placed on the head but no electricity is applied, have demonstrated the efficacy of ECT in depression, with improvements on the HAM-D of over 5 points greater than antidepressants (UK ECT Review Group, 2003).

The quality and strength of this evidence has made the conduct of such studies in older adults with depression unethical. However, studies have directly compared ECT by age. One, examining 268 adults with MDD who all had a HAM-D of greater than 20, found ECT to be of greater benefit in adults between 60 and 74 and in those 75 and over compared with younger adults (Tew et al., 1999). Another of 253 adults, again with MDD and a HAM-D score of over 20, reported ECT to be non-significantly more beneficial in adults of 47 to 64 and in those 65 and over compared with younger adults, and reported a positive correlation between symptom improvement and age (O'Connor et al., 2001). Importantly, both studies found no age-associated increase in adverse effects. A meta-analysis confirmed that ECT is more effective in older people (greater remission and response), and safe and better outcomes also occur in those with psychosis (van Diermen et al., 2018). These findings are very encouraging and support a confident use of ECT in late-life depression, though the patients in such trials were by definition those who were physically fit enough in the first place.

A clinical dilemma with ECT is what to do once someone is well again. Relapse rates after remission with ECT are high. A study in adults of all ages found continuation ECT and pharmacotherapy provided similar reductions in relapse rates, both much better than historic relapse rates on no treatment (Kellner et al., 2006). However, a limitation in this study was that ECT was a fixed ten-treatment regime that did not allow flexibility by clinical response and thus did not perhaps reflect real-world practice. A more recent large randomized trial, which included only older people with major depression, employed four continuation ECT treatments in the month following remission and then flexible further ECT determined by clinical symptoms (Kellner et al., 2016). All ECT subjects also had continuation and maintenance pharmacotherapy with venlafaxine and lithium. Encouragingly, this found that compared with continuation and maintenance pharmacotherapy alone, the ECT arm had lower depression scores and more patients who remained well. This supports the practice of many clinicians, based on experience, that

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maintenance ECT is effective in this selected group of ECT-treated patients.

Other stimulation treatments are available for depression but there is little good-quality evidence to justify their use and none specifically in late-life depression. Transcranial magnetic stimulation (TMS) has received most attention and has good evidence for efficacy in depression (Slotema et al., 2010). However, its efficacy is significantly less than that of ECT (Slotema et al., 2010) and it is therefore unclear which patients should receive it. In late-life treatment-resistant depression, one study reported benefit (Fabre et al., 2004) from TMS but another did not (Mosimann et al., 2002). TMS also has limited availability and while it is unclear which patients might be selected for its use, it is difficult to justify providing it in clinical services. Vagal nerve stimulation has some evidence for its benefit in selected patients with treatment resistance to antidepressants (Sackeim et al., 2001) but is expensive and very limited in its availability. Similarly, deep brain stimulation (DBS) is only available at a few selected centres. DBS involves surgically placing an electrode in a selected brain area (such as the nucleus accumbens or subcallosal cingulate gyrus). The electrode is connected by a wire to a neurostimulator placed subcutaneously in the chest wall which is then operated by an external device to set the frequency of stimulation. It can be effective in highly selected treatment-resistant patients (Blomstedt et al., 2011) but there are currently very few studies and there are ethical concerns about its use in depression (Synofzik and Schlaepfer, 2011). A similar group of patients might be considered for psychosurgery, which also has some evidence of benefit, but it is only available in specialist centres and attracts similar ethical concerns; DBS appears to be replacing psychosurgery in such treatment refractory patients (Sachdev and Chen, 2009).

Achieving remission in late-life depression

The clinician managing someone with depression should be aiming to achieve remission, rather than simply symptomatic improvement, and so should persist and utilize a range of strategies to achieve this and restore people to normal functioning and a symptom-free state. Persistence in applying a logical and structured approach results in over 80% achieving remission (Rush, 2007). As discussed earlier, the management strategy used should be tailored to the severity level of depression and stepped up if remission is not achieved at the starting level. But once several treatments have been utilized at different levels in the stepped care process, then a structured and persistent approach is needed to combat the danger of fatalism and despair developing and such a strategy largely involves pharmacotherapy.

First and most obviously the antidepressant can be increased in dose or prolonged in its use. When dealing with older patients there remains a tendency to use lower doses and increase them cautiously (applying the old age psychiatrist's adage of 'start low, go slow'). While appropriate

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with the frail elderly, this is probably too cautious an approach for adults who are chronologically 'old' but biologically 'young'. For example, in the open-label acute treatment phase of a maintenance study in late-life depression using citalopram it was reported that 50% of subjects tolerated 40mg and many had 60mg (Klysner et al., 2002). An additional caveat to this approach is to consider a patient's previous history and especially the risk of relapse, so that earlier and more robust treatment should be used in those with depressive episodes earlier in life whose symptoms are now returning.

How quickly should an older person with depression respond to treatment? While it is often said that it takes four to six weeks for antidepressants to work, it is important to be clear what this means and to distinguish between response and remission. Thus in general it is expected that some improvement in symptoms (that is there will be evidence of response to treatment) will occur within a couple of weeks and such early response is predictive of stable later response (van Calker et al., 2009); the disappearance of all or nearly all symptoms (remission) will take some weeks longer. But are these timelines also applicable to late-life depression? Two studies directly comparing response and remission in older and middle-aged depressed adults reported no differences (Alexopoulos et al., 1996; Reynolds et al., 1996) and a review of the literature reached the same conclusion (Whyte et al., 2004). Predictors of a slower response are greater severity of depression, comorbid anxiety and late-age at onset of the illness (Alexopoulos et al., 1996; Whyte et al., 2004). However, these encouraging findings need to be qualified by acknowledging that the underlying research was conducted in physically healthy and cognitively intact older adults who were relatively young (almost all under 80). Other data indicates neurocognitive impairment and physical illness are also associated with poorer response and remission rates. Thus, in the 'younger-old' the same approach can be taken as with younger adults but for people with these comorbidities a slower response and lower remission rates are expected. A related issue is of possible differences in EOD versus LOD. Here the evidence is mixed, with studies reporting no differences (Reynolds et al., 1998), LOD to have a worse prognosis (Alexopoulos et al., 1993b), and EOD to have poorer prognosis (Brodaty et al., 1993). While differences in the groups studied are likely to explain such discrepant findings it makes it difficult to draw firm conclusions. The wider evidence for increases in WMHs on MRI imaging in LOD (Herrmann et al., 2008) and the robust evidence associating such lesions with poorer outcomes (Alexopoulos, 2002; Alexopoulos et al., 2008; Kohler et al., 2010b; O'Brien et al., 1998) leads the author to conclude LOD responds more slowly, and this is corroborated by clinical experience.

How long should you wait before adjusting antidepressant treatment? In 'younger-old' people with late-life depression then if there is no apparent change at all by two weeks then, assuming no adverse effects, the dose should be increased and increased to the maximum tolerated dose. In

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those with LOD and/or with cognitive impairment and/or physical morbidity it is prudent to wait until perhaps four weeks. If there is symptom improvement then treatment should be continued and the dose increased if further improvement ceases. An important factor is duration of treatment since it has been shown that the longer a trial lasts the greater the difference between drug and placebo; that is, when a trial is conducted over a longer period a larger proportion of people achieve response and more importantly remission on medication, thereby creating a larger difference from placebo and clearer evidence of benefit. Thus in a systematic analysis of this it was reported that in clinical trials of six to eight weeks' duration the odds ratio in favour of antidepressants was 1.2, whereas in those studies with outcomes at between ten and 12 weeks after baseline, the odds ratio was substantially increased to 1.73 (Nelson et al., 2008). Such evidence supports persistence with a treatment rather than quickly switching to an alternative because improvement seems to be too slow. In practice, a treating doctor can come under both internal ('I need to do something') and external pressure to change treatment and is then in danger of losing gains by switching to an alternative or unnecessarily adding in a new treatment through impatience, thereby exposing the patient to a higher risk of adverse effects. Patient explanation and support and utilization of other aspects of treatment, e.g. group activity or problem-solving therapy, are perhaps better responses in such circumstances. Switching to an alternative antidepressant should be carried out as soon as it is clear no benefit at all is being achieved (if some benefit is apparent then augmentation or combination approaches are indicated) or more commonly when adverse effects preclude its continuation.

If the strategies of increasing the dose and prolonging the duration of treatment are not successful and remission is not achieved on the maximum tolerated dose then combination and augmentation strategies should be considered. Unfortunately, as with switching and increasing the dose, the evidence for such strategies is limited. A combination approach (adding a second antidepressant) is very popular but has little empirical evidence to support it. Clinical experience supports it and a popular combination involves adding mirtazapine to an SSRI, since the latter is in most cases the initial antidepressant. For the pharmacological reasons discussed above this is rational strategy and experience suggests it is frequently helpful. Again, the mirtazapine, or other combination agent, should be increased to the maximum tolerated dose and other treatment aspects (group CBT, anxiety management, etc) explored during this treatment phase.

The alternative is to augment the first line antidepressant with a non-antidepressant. The best evidence is for antipsychotic augmentation with a well-designed study randomizing 181 people who did not remit on venlafaxine (and in most cases a pre-trial SSRI) to aripiprazole or placebo augmentation (Lenze et al., 2015). They found that by four months significantly more people remitted on aripiprazole compared with placebo

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(44% vs 29%), which is clinically important with a Number Needed to Treat of 6.6. the aripiprazole was generally well tolerated, with most people being on 6–10mg and having fewer dropouts than in the placebo arm. More people did develop parkinsonism and akathisia on aripiprazole, but a careful assessment of weight, lipid, and cardiac profiles showed no differences from placebo. The propensity of aripiprazole to increase agitation and akathisia may be problematic in older people for whom anxiety/agitation is part of the clinical presentation, and in such cases an alternative antipsychotic with more sedative properties, e.g. olanzapine, may be preferred.

Historically lithium has been the most frequently used augmentation agent. There is evidence to support this, though mainly from smaller, lower-quality studies (Crossley et al., 2007), including replicated evidence of benefit in late-life depression (Cooper et al., 2011). However, lithium has well-recognized adverse effects and it is not clear what serum level of lithium is appropriate for augmentation. Generally, in older adults one should aim for lower lithium doses and lower serum levels of around 0.4mmol/L, but this is mainly driven by a desire to avoid or minimize adverse effects rather than by empirical evidence. Older patients appear especially susceptible to lithium side-effects with one study reporting polydipsia (50–74%), polyuria (25–58%), tremor (33–58%), and dry mouth (53%) as the most frequent adverse effects, but a worryingly large percentage (11–23%) developed lithium toxicity (Foster, 1992). In the author's experience, tremor can be particularly problematic and disabling and although dosage reduction often helps, in some cases it prohibits continued use of lithium. Lithium augmentation has become less popular, probably because of the extra effort involved in monitoring and these concerns about toxicity, and because of the development of additional classes of antidepressants encouraging combination strategies ahead of augmentation. One well-designed study has examined 'augmentation' in late-life depression, though since the 'augmentation' agents used included nortriptyline and bupropion (as well as lithium), it really assessed both combination and augmentation. These second-line treatments were added to paroxetine (combined with IPT) and encouragingly an extra 20% (over half those receiving 'augmentation') then achieved recovery (Dew et al., 2007). The cholinesterase inhibitor donepezil has also been studied as an augmentation strategy in late-life depression, though only as an add-on in the maintenance phase. Unfortunately, it was found that, while donepezil produced some modest and transient improvements in cognition, its use was associated with a significantly higher relapse rate (Reynolds et al., 2011). Methylphenidate has also been investigated in a complex study when it was added to citalopram (Lavretsky et al., 2015). Augmentation with methylphenidate produced possible modest improvements compared with monotherapy, but interpretation of the findings is difficult due to the absence of a placebo arm.

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Beyond augmentation and combination with single agents there are options of adding in other augmentation and antidepressant agents. Evidence from the STAR-D study suggests, as might be expected, a law of diminishing returns applies as more treatments are added, but that remission can be achieved in about 80% (Menza, 2006), with similar results in studies of late-life depression alone (Cooper et al., 2011). However, this does leave 20%, a considerable proportion, who remain unwell, and in such treatment-resistant subjects it is prudent to revisit the diagnosis, considering for example the extent to which persistent symptoms may be related to a physical illness or a personality disorder. At this point ECT should also be considered, if it has not already been employed earlier due to severity and persistence of depression. After soliciting a second opinion, the more exotic stimulation and surgical treatment options might be investigated.

Continuation and maintenance treatment

Once remission is achieved the clinical issue becomes keeping the patient well. It is clear that in a first episode of depression the successful treatment should be continued (Geddes et al., 2003). Since the risk of relapse is highest in the first six months this continuation treatment should be for at least six to nine months for a first uncomplicated episode from when they achieve remission, and for at least in year in other situations (Cleare et al., 2015). In younger adults, maintenance treatment (that is, continuation of antidepressant treatment beyond this continuation phase) is not recommended after a single episode of depression, but the situation is different for older adults. Full-dose maintenance treatment is effective, with evidence supporting its use up to three years. Several of the key studies have specifically been conducted in late-life depression and a meta-analysis of eight double blind trials reported the number needed to treat to prevent one additional relapse or recurrence to be only three (Kok et al., 2011).

These maintenance studies highlighted that, even in those with a first episode of LOD, the risk of relapse after treatment is stopped is very high—an important issue familiar to those working with older people with depression. When one cohort of such LOD patients was followed-up when treatment was stopped after two years, over 60% had a further episode in the following two years (Flint and Rifat, 1999). When considering maintenance treatment, the impact of another depressive episode should be weighed, and in older people with relatively few remaining years the impact is disproportionately high. The consideration in younger adults about exposing someone for many years to unnecessary antidepressant treatment does not apply. Thus, in general, even when someone has a first episode of LOD, they should be put on maintenance treatment and, by extension, so should all people with late-life depression. As evidence from studies of major depressive disorder shows, the important caveat to this is that for those with less severe depression who have received antidepressants, such long-term use might not be warranted.

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When planning continuation (and especially maintenance treatment) education of the patient and significant others about illness and the risk of future relapse is crucial. Many older patients are reluctant to take medication, especially antidepressants, and many stop taking the medication when they feel well. Thus, discussing the impact of the illness, the benefits of antidepressants, explaining the high risk of relapse, and how this risk can be substantially reduced by taking antidepressants long-term is vital. By engaging the patient in managing the illness we can maximize the likelihood of long-term adherence to treatment.

Most of the literature has examined maintenance pharmacotherapy, but two major studies have examined interpersonal therapy (IPT), both alone and in combination with maintenance drug treatment, for maintenance in late-life depression. Monthly IPT was reported in the first study to reduce relapse rates compared with routine follow-up, and combined IPT and nortriptyline was even more effective (Reynolds et al., 1999). However, the second study, involving the same design but substituting paroxetine for nortriptyline, found no benefit of IPT alone or in combination in the maintenance phase (Reynolds et al., 2006). It is worth noting, however, that this second study was on patients who on average were about ten years older and included a significant proportion with LOD, which may have reduced the potential benefit from IPT.

Depression in the context of other illnesses

Depression is highly prevalent in association with physical illness in general and with specific (brain) disorders, e.g. PD, in particular. The difficulty diagnosing depression as a separate entity when other illnesses are present was discussed earlier. Antidepressants are frequently prescribed in such circumstances in spite of the diagnostic difficulties, but evidence supporting their use in such situations is limited. An analysis of one large maintenance trial in outpatients reported that a high burden of physical illness predicted a higher depression recurrence rate (Reynolds et al., 2006) and this also applied to augmentation (Dew et al., 2007).

Depression in dementia is frequent and major issue and different classes of antidepressants have been tried in several clinical trials. However, these trials were often of poor quality and conducted in small numbers of subjects. Thus, while systematic reviews found no evidence of benefit from using antidepressants, these conclusions were recognized to be subject to a type 2 error. But two large studies found no benefit from using antidepressants in people with depression in the context of dementia. DIADS-2, a multicentre US randomized trial of sertraline 100mg versus placebo in depression in AD, found no evidence of improvement in symptoms, response rates, or remission rates on sertraline at either 12 weeks (Rosenberg et al., 2010) or 24 weeks (Weintraub et al., 2010). Furthermore, those on sertraline suffered a higher frequency of adverse effects. The UK SADD study was a nine-month randomized study at nine centres across England and compared

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sertraline, mirtazapine, and placebo for depression in dementia; it also reported no evidence of benefit from either antidepressant but an increase in adverse effects on medication (Banerjee et al., 2011). These findings strongly caution against the widespread use of antidepressants for depression occurring in people with dementia. However, these studies necessarily did not include people with more severe depression, including those at significant suicide risk, for whom antidepressants might still be appropriate; this is especially the case if there is a previous history of major depression.

Studies of antidepressants in stroke disease have reported evidence of efficacy but this is offset by an increase in adverse effects in those on antidepressants (Hackett et al., 2008). Thus, the clinician needs to carefully weigh up the potential benefits, determined by the severity of the current depressive episode and the history of previous episodes of depression and their response to treatment, with these risks of adverse events. Three randomized trials of psychotherapy in post-stroke depression found no evidence of benefit on any outcomes (Hackett et al., 2008). SSRIs are the most appropriate antidepressant to use in post-stroke depression, not only because the best evidence from trials is for this drug class, but also because they have been demonstrated to be safe to use in people with coronary heart disease and, by extension, vascular disease more broadly (Glassman et al., 2002). As with the management of major depressive disorder, the key issue is when to initiate such treatment, given the need to balance exposure to predictable adverse drug effects with potential benefits on mood. Again, when depressive symptoms are not severe or persistent it seems prudent to withhold medication as the risk/benefit ratio is likely to be unfavourable, and because spontaneous remission is common in this group. Conversely, if a post-stroke depression is severe or persistent then SSRIs should be initiated, closely monitored, and titrated to achieve maximum effect.

Post-stroke emotionalism is often confused with depression. Here, people with stroke disease have outbursts of tearfulness, or more rarely euphoria and laughter, which are triggered by insignificant emotional stimuli or no apparent stimuli. Unlike depression, the mood changes are rapid and typically not associated with the appropriate subjective emotional experience, e.g. they don't feel sad while crying. Although not well characterized or recognized in psychiatric classifications, it is a frequently encountered clinical problem and antidepressants have been studied in small trials. Overall, all classes of antidepressants seem to produce significant benefits, which typically occur more rapidly than with response in depressive disorders (Hackett et al., 2010).

There have also been few studies investigating the benefits of treatment of depression occurring in PD. As with early studies in depression in dementia, the few studies have been small and produced equivocal results. The Cochrane review reported no evidence of benefit from CBT or ECT and equivocal evidence for antidepressants (Ghazi-Noori et al., 2003). However, this was based on three small antidepressant trials and

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since this, two larger studies have been reported. The first, in 52 subjects, found nortriptyline to produce larger improvements in depression symptoms than either paroxetine or placebo over eight weeks (Menza et al., 2009). The other in 287 people found pramipexole produced a statistically greater, but clinically unimportant (<2 point difference), improvement on the Beck Depression Inventory at 12 weeks than placebo. But there were no differences on the Geriatric Depression Scale and of note is that depression was defined as having a low GDS score of only >5 (Bxarone et al., 2010). Currently it is not clear whether antidepressants or antiparkinson's treatments produce significant clinical benefits for people with depression in PD.

Prevention of late-life depression

Since depression is so highly prevalent there has been increasing interest in preventing the development of depression, including late-life depression, in the first place (Beekman et al., 2010; Cuijpers et al., 2008). Unsurprisingly, strategies aimed at the general population (universal prevention) do not appear effective (Beekman et al., 2010), but those targeting older people with subthreshold depressive symptoms do reduce the development of depressive and anxiety episodes at both one year (van't Veer-Tazelaar et al., 2009) and two years (van't Veer-Tazelaar et al., 2011). Targeting high-risk individuals (those living alone, having two or more chronic illnesses, significant anxiety symptoms, lack of mastery over their environment) also appears to reduce the development of depressive syndromes (Smits et al., 2008). With both 'high risk' and 'subthreshold' groups, depression was reduced in primary care settings by 'watchful waiting' followed by bibliotherapy, problem-solving therapy, and, if necessary, medication. A review of nonpharmacological approaches to depression prevention suggested modest effectiveness with a NNT of 20 (van Zoonen et al., 2014).

Prognosis in late-life depression

In contrast to outcome findings from research, which are based on aggregated data from follow-up studies on cohorts of patients, the clinician is usually asked to predict the prognosis for a *specific* patient with his *unique* combination of individual characteristics. Such a transformation requires combining a knowledge of the relevant research findings, familiarity with the specific patient's features, and the wisdom acquired from clinical experience; it is an area where such medicine-based evidence is especially required to modify the research-driven evidence. In theory, outcome data would come from both naturalistic studies of treatment-free patients and from treatment studies prospectively examining outcomes. In practice there is very little purely naturalistic data available and what was reported (e.g. Post, 1972), emanated from specialist inpatient units making it difficult to compare with later data derived from very different clinical settings.

Outcome of depression

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Reports from studies examining outcome comment on both the high mortality in late-life depression and the generally poor prognosis. For example, a meta-analysis of community depression in older people (mean age over 60) involving a total of 1,268 patients found that at two years after the index episode of depression, 33% were well, 33% were still depressed, and 21% were dead. The rest were classified as 'other' and appeared to represent a poor outcome group, including people who developed dementia and had only partial remissions (Cole et al., 1999). Although most of the studies had weaknesses, the two largest and best executed studies reported similar findings (Copeland et al., 1992; Kennedy et al., 1991). A more detailed prospective analysis of community depression over six years and including 14 assessments had more encouraging, though still poor, findings (Beekman et al., 2002), with 23% having persistent remission, 12% remission with recurrence, 33% a chronic-intermittent course, and 33% had chronic depression. They also reported that outcome was related to baseline diagnosis with sub-threshold depression having the best outcome, major depression and dysthymia intermediate outcomes, and 'double depression' (major depression on top of dysthymia) having the poorest outcome. Older primary care patients with depression were found to have episodes lasting a median of 18 months and after one year of illness only 35% were well; by two years 60% and by three years 68%. Physical ill health and depression severity at baseline were predictors of poor outcome (Licht-Strunk et al., 2009), as was also reported by a longitudinal study in the Netherlands (Comijs et al., 2015). Bleak conclusions were also reached in another meta-analysis of elderly medical inpatients with depression (Cole and Bellavance, 1997a). At three months only 18% were rated as well, 43% were still depressed, and 22% were dead; by 12 months only 1% were well, 29% still depressed, and 53% had died. However, there are clearly difficulties in interpreting such data and distinguishing physical illness causes from any additional depression effect. A detailed analysis controlling for physical illness, comorbidity, and previous history of depression found no increase in mortality for those diagnosed as depressed during their hospital admission; this study also found that after taking these factors into account, pre-existing depression was associated with a reduced mortality (McCusker et al., 2006). For psychiatrists there is some encouragement from a third analysis by these authors reporting better outcomes in people with late-life depression who were seen by hospital psychiatric services (Cole and Bellavance, 1997b). This analysis of 1,487 patients in 16 studies followed for at least a year found 60% were either well or had relapses with good recovery, 14–22% were continuously ill, with the remainder again having poor outcomes such as death (ranging from 3% to 19% dead by twelve months) or developing dementia. Again, although many of the studies had weaknesses, the overall findings are similar to those in the larger and better executed studies in the analysis (Baldwin et al., 1993; Baldwin and Jolley, 1986; Burvill et al., 1991). While the mortality in medical inpatients is unsurprising (and is not clearly directly related to depression in any case) the poor outcome in community psychiatric patients compared with

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psychiatric secondary care patients is counter-intuitive as the former are expected to have milder forms of depression and thus better outcomes than patients referred to psychiatric services. This may reflect under detection and under treatment in the community with reports indicating only 20% (Cole et al., 1999) and 10% (Sharma et al., 1998) of depressed older people in the community receiving adequate treatment.

Subsyndromal forms of depression have a high conversion rate to major depression in older people—about 8% per year—and while having better overall outcomes than major depression, such conditions still remit by one year in only about 27% (Meeks et al., 2011).

That depression in older people is associated with an increased mortality has been long recognized, e.g. a threefold increase (Murphy et al., 1988), but is depression itself the cause of this? Several studies have investigated this question by following depressed older patients over several years and controlling for other risk factors. A Finnish study examined 813 subjects over five years and found 48% of those depressed at the beginning and end of the study had died, compared to only 26% who were never depressed, but those who were only depressed at baseline did not differ significantly (31% mortality) (Pulska et al., 1999). A four-year study from the Netherlands found those with major depression had a significant 1.83-fold increase in mortality, while only men with minor depression had a significant increase (1.80-fold) (Penninx et al., 1999). The same group reported similar findings in another cohort of 4,051 community-dwelling older people who were followed over six years (Schoevers et al., 2000). Survival analysis showed only men with 'neurotic' depression had a significant increase in mortality of 1.67-fold while both men and women with 'psychotic' depression (approximately major depression) had significant increases in mortality of about twofold. A US study following older people with broadly defined depression (20% had depression) over six years found a 24% increase in all-cause mortality in this depressed group after controlling extensively for other risk factors for mortality (Schulz et al., 2000). A ten-year prospective study in the Netherlands of 3,746 community-dwelling subjects with depression confirmed the increased mortality and reported a dose-response relationship, whereby more severe and more chronic depression was positively correlated with this increased risk (Schoevers et al., 2009).

Such studies uniformly confirm the high mortality associated with late-life depression, whether major or minor depression, and suggest men may have a higher risk; this increase seems to be due to depression itself, rather than confounding factors associated with depression. The strong relationship of depression to cardiovascular and cerebrovascular disease is likely to be an important factor in this relationship.

These findings would suggest that depression in older people has a poorer response to treatment than depression in younger adults and makes the findings from a review of this issue somewhat surprising. Reviewing 24 publications between 1996 and 2004 Mitchell and Subramaniam (2005) reported that depression remitted as frequently in

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later life but was associated with a higher relapse rate. This increased risk of relapse was linked to age at onset of depression, with EOD having a poorer outcome because of multiple episodes in earlier life, and medical comorbidity, which worsened prognosis and was linked to a later onset).

Prognostic factors

Box 39.4 summarizes several poor prognostic indicators recognized in late-life depression. The presence of such factors should not lead to under-treatment or pessimism, but rather should encourage a more vigorous approach to treatment. Unsurprisingly, physical illness burden (Azar et al., 2011; Reynolds et al., 2006; Baldwin and Jolley, 1986; Burvill et al., 1991; Murphy, 1983; Licht-Strunk et al., 2009), depression severity (Licht-Strunk et al., 2009; Azar et al., 2011; Reynolds et al., 2006), comorbid anxiety (Azar et al., 2011; Reynolds et al., 2006), and cognitive impairment (Cole and Bellavance, 1997b; Nelson et al., 2008) have been associated with a worse outcome in late-life depression and clinically significant cognitive impairment is strongly associated with an increased risk over the following few years of dementia (Alexopoulos et al., 1993a). The only other consistent predictors of outcome have been discussed earlier, namely ischaemic WMHs and executive dysfunction. WMHs and related white matter changes leading to increased diffusion are associated with a poorer response to antidepressants (Alexopoulos et al., 2002; Alexopoulos et al., 2008), poorer longer-term outcome and increased relapse rates (Hickie et al., 1996; O'Brien et al., 1998), and persistent cognitive impairment up to four years (Kohler et al., 2010b). Executive dysfunction predicts poorer response to antidepressants and increased relapse rates (Alexopoulos et al., 2000; Kalayam and Alexopoulos, 1999; Sneed et al., 2010).

Box 39.4 Poor outcome predictors

- Physical ill health
- Depression severity
- Chronicity of depression
- Presence of white matter hyperintensities
- Cognitive impairment (especially executive dysfunction)

Other factors examined do not seem to predict outcome. Once confounding factors have been accounted for, there appear to be no consistent differences due to sex or age. Depression severity and duration were reported in one study to predict poorer outcome (Murphy, 1983) but other studies have not replicated this (e.g. Baldwin and Jolley, 1986; Burvill et al., 1991). Murphy (1983) reported that adverse life events after

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the onset of depression predicted poor outcome, but Burvill and colleagues (1991) assessing this did not show the same results. Again, Murphy (1983) found the occurrence of adverse life events following the onset of depression had a particularly adverse effect on outcome, where Burvill and colleagues (1991) found no such relationship.

Conclusion

Depression in late life remains common and has a similar symptom profile to that in younger adults, but the elderly tend to have more psychosis and cognitive impairments. The relative contributions of the proposed aetiologies need to be more precisely defined. Although factors such as adverse life events and social isolation remain important, physical illness, vascular brain disease, and other subtle organic factors become important, too, especially for those with LOD. Antidepressants are as effective in the 'younger-old' (those without clinically significant cognitive impairments or physical illness) as in younger adults, but probably less so for those afflicted by such comorbidities. ECT remains an effective and safe treatment in the elderly. The evidence supporting benefits from specific psychotherapies is limited, though for the 'younger-old' they probably remain as useful as in younger adults and multifaceted interventions involving care management applications of several interventions appear highly effective. Continuation and maintenance use of antidepressants is effective in reducing relapse and should probably be used in all late-life major depression. Longer-term outcome is poor in naturalistic studies but much improved in treated patients. A high (two- to threefold increase) mortality is evident and depression is an important risk factor for subsequent dementia. All this highlights the need for careful detection and thorough assessment of depression in later life, combined with vigorous treatment and regular follow-up to monitor maintenance treatment.

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Suicide and attempted suicide in older people

Chapter: Suicide and attempted suicide in older people

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Introduction

Suicide rates vary considerably across age groups, genders, races/ethnicities, socioeconomic groups, residences (urban/rural), countries, regions, and over time (Chang et al., 2014; Ivey-Stephenson et al., 2017; Snowden et al., 2017; Värnik, 2012; World Health Organization, 2014). In most nations of the world, the risk of suicide increases with age, particularly for older men (WHO, 2014). The magnitude of this global public health challenge will escalate rapidly with the anticipated worldwide burgeoning of the older population. Another factor highlighted by some researchers is the cohort effect from baby boomers, who may have a higher rate of suicide than their predecessors entering old age after the first decade of the millennium (Conwell et al., 2002a; Phillips et al., 2010). This chapter first examines the scope of the problem and, from a public health perspective, addresses the risk and protective factors related to suicidal behaviours in late life, upon which evidence-based prevention and intervention ('postvention') measures might be mounted

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at accessible points along the suicide trajectory (Conwell et al., 2011). It reviews the available studies that have looked at possibilities for prevention of suicide in older people around the world.

Epidemiology and trends

Completed suicide

Geographical and demographic variations in suicide

In 2015, around 26% of the 0.8 million completed suicides in the world occurred in adults aged 60 years and above, with males being predominant (62.2%) (World Health Organization, 2016). Of those elderly suicide events, 45.3% and 15.9% took place in the WHO Western Pacific Region and South-East Asia Region, respectively. Considering nation states, China (34.9%), India (10.6%), United States (5.8%), Japan (5.0%), Russia (3.0%), and South Korea (3.0%) were the top six contributors to the total number of elderly suicide deaths worldwide (World Health Organization, 2016). According to the 2016 Global Burden of Disease Study (GBD) (Global Burden of Disease Collaborative Network, 2017), suicide rates in people 70 and over were generally lowest in North Africa and Middle East and Central and Andean Latin America, and highest in East Asia, the Asia Pacific region, and Sub-Saharan Africa.

In 2000–2015, the total number of global elderly suicides increased by 26.9%, which was mostly due to the substantial increase in the WHO Western Pacific Region and South-East Asia Region (Fig. 40.1). (World Health Organization, 2016).

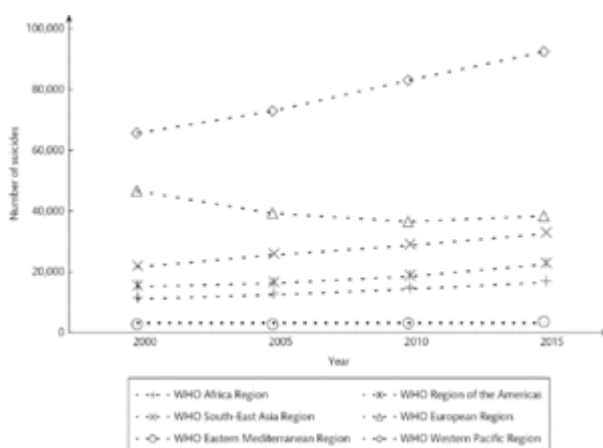


Fig. 40.1

Total number of 60+ elderly suicide instances in the world, 2000–2015.

Source: data from World Health Organization, mortality estimates by cause, age and sex, globally and by region, 2000–2015, http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html.

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Considering individual countries and regions, in 2013–2014, the suicide rate in adults aged 65+ was estimated to be 34.5 per 100,000 in mainland China, which was lower than South Korea (58.7) but higher than Taiwan (30.7), Japan (24.4), Hong Kong (21.0), Singapore (21.1), United States (17.2), Australia (12.0), United Kingdom (8.5), and Germany (21.4), when rates in these jurisdictions were standardized to the 2014 Chinese population (Zhong et al., 2016b).

Globally, rates of suicide for both men and women are generally higher in older than younger age-groups, and this is particularly evident in males (Fig. 40.2) (Global Burden of Disease Collaborative Network, 2017; Sachs-Ericsson et al., 2016; Zhong et al., 2016b). However, the pattern varies across countries. For example, in 2015, in the United States (US), Canada, and Australia, suicide rates peaked in mid-life for females and declined slightly thereafter (Global Burden of Disease Collaborative Network, 2017); or, in 2010, among Indian men in the US, suicide rates peaked in young adulthood, then declined progressively with age (Conwell, 2014).

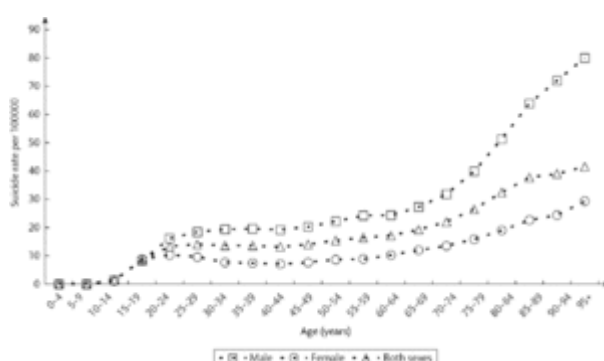


Fig. 40.2

Rates of suicide in older people by quinquennial age-group and gender in the world, 2015.

Source: data from Institute for Health Metrics and Evaluation (IHME), Global Burden of Disease Study 2016 (GBD 2016) Results, 2017, <http://ghdx.healthdata.org/gbd-results-tool>.

Based on the suicide mortality data provided by the GBD 2016 and world population data provided by the United Nations (Global Burden of Disease Collaborative Network, 2017; United Nations, 2015a), the global suicide rate in people 60 years or older was estimated to be 22.2 per 100,000 in 2015, 32.1 in men and 13.7 in women, with a 2.3 male-to-female ratio. Worldwide, older men have a higher of suicide mortality rate than older women, but there are wide variations in the male-to-female ratios between countries (Alves et al., 2014; Shah, 2007): for example, 5.8 in the US compared to 1.4 in China (Zhong et al., 2016b).

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Time-trends

Adults aged 60 or above comprised 12% of the world's population in 2015 (United Nations, 2015b) but they accounted for 26% of the total suicide deaths, showing that suicides are over-represented in older adults. Furthermore, the proportions of elderly suicides within all suicide events increased from 22% in 2000 to 26% in 2015. In contrast, the proportions of suicide deaths occurring in young people (15–29 years of age) had decreased from 32% to 28% during the same period (World Health Organization, 2016). In some countries like China, the proportion of all suicide deaths occurring in people aged 65 or above had greatly risen from 17% in 1987 to 41% in 2014 (Zhong et al., 2016a).

Worldwide, the overall time-trend in elderly suicide rates is downward from 2000 to 2015 (Fig. 40.3) (Global Burden of Disease Collaborative Network, 2017).

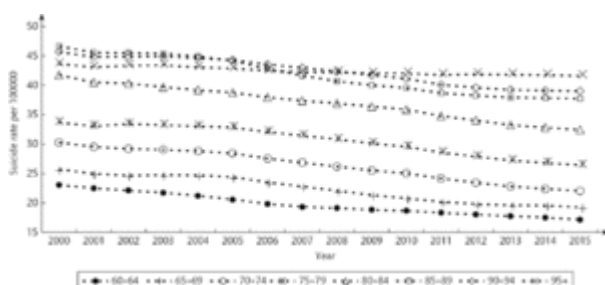


Fig. 40.3

Rates of suicide in older people by quinquennial age-groups in the world, 1990–2015.

Source: data from Institute for Health Metrics and Evaluation (IHME), Global Burden of Disease Study 2016 (GBD 2016) Results, 2017, <http://ghdx.healthdata.org/gbd-results-tool>) +H86:K86.

Similar time trends have been ascertained in individual regions such as mainland China and Cuba (Corona-Miranda et al, 2016; Zhong et al., 2016a), but the changing patterns vary between countries, for example, the elderly suicide rates in Cuba increased with time before 1993 and declined thereafter while the rates in China remained stable before 1998 and dramatically decreased thereafter. In contrast, in South Korea suicide rates in people 70 or over significantly increased from 29.9 per 100,000 in 1990 to 99.5 in 2010 followed by a decrease to 89.0 in 2015. It is noteworthy that some major social changes can influence the time-trend in elderly suicide rates, for example, in Sri Lanka, the restrictions on the import and sales of WHO Class I toxicity pesticides in 1995 and endosulfan in 1998, are believed to have successfully reversed the upward trend before 1995 to a downward trend thereafter in elderly suicide rates (Gunnell et al., 2007). On the other hand, in 45 European and American countries, suicide rates in male older adults significantly

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increased in 2009 after the 2008 global economic crisis (Chang et al., 2013).

However, caution is necessary when comparing suicide statistics across countries. First, there is a lack of reliable surveillance systems in some low- and middle-income countries. Even for the WHO databank on mortality, there is scarce information on suicide data from some regions of the world (Beautrais, 2006). Second, for some countries like India, suicide statistics are collected from a small percentage of the population, which may influence the accuracy of the data. Third, there are variations in the practice of ascertaining a death as suicide in different countries. In countries with a coroner system, the extent of the use of 'open verdicts' and 'narrative verdicts' are likely to influence the number of deaths recorded as suicide. For instance, a narrative verdict may describe the circumstances of the death briefly without attributing the death to a category such as suicide (Carroll et al., 2012).

Cohort and period effects

Some authors have speculated that cohort effects (the ensemble of environmental factors that connote a certain generation and its relative size; see De Leo, 2002) may further accentuate suicide rates for older age groups in the foreseeable future (Conwell et al., 2002a). Higher suicide rates have been identified in the generations born in the fertile post-war decades in the US (Conwell et al., 2010) and in 18 European nations (Pampel, 1996), especially among men. Suicide rates tend to be higher in those age groups that comprise larger proportions of the total population, perhaps because of increased competition for scarce societal resources (Lindesay, 1991). However, because of different cultural influences, this cohort effect is unlikely to be universally applicable across countries (De Leo, 2002), and further studies are needed to examine the impact on trends in suicide rates at older age ranges. Period effects (e.g. from wars or major catastrophes experienced by the whole population at the same time) on suicide rates among older people are even less well understood. In Hong Kong, during the community outbreak of severe acute respiratory syndrome (SARS) in 2003, the older suicide rate in Hong Kong showed a sharp upturn from a previous downward trend, particularly in older women. It was postulated that factors such as the breakdown of social networks and limited access to healthcare might account for the findings: older women, because of their previous readiness to utilize social and health services instituted in the past decade, might have been more susceptible to the effects of temporary suspension of these socially supportive services during the epidemic (Chan et al., 2006).

Attempted suicide

There is very limited epidemiologic data on attempted suicide in old age, as, unlike completed suicide, there is usually no systematic registry for such events, even in the most developed countries. Attempted suicide is

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far less frequent in later life than among younger age groups (Mościcki, 1997, 2001). In adolescents, the ratio of attempted to completed suicide has been estimated to be 200:1. In contrast, there are estimated to be approximately four attempts for each completed suicide in later life (Conwell, et al., 2002a). Contributory factors to the increased lethality of self-harm behaviours in older people include higher levels of planning and resolve, the violence of methods used, diminished physical resilience, and greater social isolation (thus lower chance of timely availability of medical interventions), as well as potentially a reluctance to express or endorse suicide ideations (Conwell et al., 2002a). In a controlled retrospective study of older people completing suicide, those attempting suicide, and community controls, it was further shown that those completing suicide and hospital-treated attempters were largely overlapping populations and their acts were driven by very similar spectra of risk factors. This is different from the situation in younger counterparts, where major disparities have been found in sociodemographic factors and diagnoses (Tsoh et al., 2005). Furthermore, it adds to the evidence that in late life, preceding suicide attempt is among the strongest predictors for subsequent suicide (Beautrais, 2002; Waern et al., 2002a; Chiu et al., 2004; Conwell et al., 2010). Both findings show the need for high vigilance in the management of all cases of deliberate self-harm in older people.

Risk and protective factors for suicide in older adults

To understand and prevent suicide in older people, it is important to explore the related risk and protective factors from a public health perspective. Such factors are often identified through retrospective case-controlled 'psychological autopsy' (PA) studies. In PA research, information about suicide decedents is gathered retrospectively from relatives and other informants familiar with the decedents, as well as perusal of medical records (Hawton et al., 1998). Despite its limitations, such as its retrospective nature and the potential for reporting bias, case-controlled PA studies around the globe in the past 15 years have been striking in the consistency of the array of factors associated with suicide in older people (Harwood et al., 2001; Beautrais, 2002; Waern, et al., 2002a; Chiu et al., 2004; Conwell et al., 2010; De Leo et al., 2013) (see Table 40.1 for details).

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Table 40.1 Odds ratios (OR) for suicide for risk and protective factors in different domains that are statistically significant in case-controlled psychological autopsy (PA) studies of older adults.

	Harwood et al., (2001)	Beautrais (2002)	Waern et al., (2002a, 2002b)	Chiu et al., (2004); Tsoh et al., (2005)	Conwell et al., (2010)	De Leo et al., (2013)
<i>Location</i>	Central England	New Zealand	Goteborg, Sweden	Hong Kong, China	Monroe and Onondaga Counties, New York, US	Queensland and New South Wales, Australia
<i>Age</i>	≥ 60	≥ 55	≥ 65	≥ 60	≥ 50	≥ 60
<i>Sample size</i>	100	31	85	70	86	73
OR of risk/protective factors						
Mental health						
Any mood disorder	4	184.6	63.1	59.2	47.7	
Major depressive episode	–	–	28.6	36.3	12.2	
Substance abuse disorder	ns	4.4	43.1	ns	ns	

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Dementia	0.2	ns	ns	ns	ns	
Past suicide attempts	-	41.9	-	18.9	13.6	30.1
Statements of hopelessness in the past 12 months						9.4
<i>Personality</i>						
NEO Personality Inventory domains	-	-	-	Neuroticism: 1.2	-	
				Extraversion: 0.8		
						OTE: 0.8
				Conscientiousness: 0.8		
Any personality disorder	4	-	-	-	-	
<i>Physical health</i>						
Any serious medical condition	-	19.4	Men: 4.2	-	-	
			Women: 2.1			

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			Overall: 3.0			
Perceived poor health	-	1.6	-	-	-	
Number of physical conditions	-	-	-	1.9	-	
Recent hospitalization	-	25.8 (hospitalization in the past year)	-	6.8 (hospitalization in the past three months)	-	
IADL score	-	-	-	0.2	-	
Physical Self Maintenance Scale (PSMS) score						0.6
<i>Social factors</i>						
Number of recent (past six months) major life events	-	-		-	4	-
Family discord	-	17.2		-	41	-

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Serious financial problems				-	ns	-
Low social interaction				-	-	-
Poor social network (LSNS)				-	1.1	-
Living alone						
Other factors						
Living with children				-	0.5	-
Religion considered salient				-	0.2	-

IADL, instrumental activities of daily living (in the adapted version in Hong Kong, a lower score indicates worse functional level); LSNS, Lubben Social Network Scale; ns, not statistically significant; OTE, openness to experience.

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Other methods for ascertaining risk and protective factors of suicide include prospective follow-up studies of high-risk subjects (e.g. individuals with depression and those attempting suicide) and case-control studies of older people attempting suicide (as their profiles resemble those whose acts are fatal). The former are often limited by a low base rate of suicide and lack of statistical power to quantify the effect size of the putative risk factors. The latter are limited generally by the lack of systematic registries for suicide attempts. Nonetheless, these observational studies have indicated that suicidal behaviours in seniors are multi-determined. The following domains of risk and protective factors have been consistently identified: mental health, personality, physical diseases, social factors (e.g. network and support, life events), functional levels, and a range of miscellaneous others, including access to lethal means and neurobiological factors (Conwell and Thompson, 2008; Conwell, et al., 2011; Van Orden and Conwell, 2011; Conwell, 2014).

Mental health

In a systematic review of global data from controlled PA studies on suicide in older people, Conwell et al., (2011) reported that of all factors examined, psychiatric illness was consistently found to be most prominent: it is present in 71–97% of suicide cases, with affective disorder being the most common (with odds ratio (OR) of 48–185 in relation to community controls) and with major depressive disorders particularly implicated. However, in a controlled PA study, hopelessness, a pertinent depressive symptom, also stood out as a predictive factor (De Leo et al., 2013).

Psychotic disorders, including schizophrenia, schizoaffective disorder, and delusional disorder, as well as anxiety disorder, tend to be present in lower proportions of cases, unlike suicide investigations among younger populations. Furthermore, the prevalence of comorbid substance use disorder has been highly variable in these studies, although this might be related to the different rates of problem drinking in Oriental and western populations (Chiu, et al., 2004; Waern et al., 2002a; Conwell, et al., 2010, 2011).

Despite the prevalence of dementia in old age, it is infrequently diagnosed in completed suicide using the PA method, which is likely related to intrinsic methodological limitations, as the clinical picture of dementia, particularly in the early course, is less likely to be recognized by family members and other informants (Conwell et al., 2011). There are biological (Rubio et al., 2001) and epidemiological (Erlangsen et al., 2008) data that support the notion that dementia is associated with an amplified risk of suicide in late life. A recent systematic review focusing on Alzheimer's disease also echoes this finding (Serafini et al., 2016). Furthermore, a nationwide longitudinal study in Denmark of persons aged 50 and over found that in both genders, the diagnosis of dementia upon hospitalization was associated with a significantly elevated risk of

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completed suicide (especially in the first few years after the diagnosis was made) in the ten-year study period (Erlangsen et al., 2008).

A history of past attempted suicide is a significant risk factor for future completed suicide (e.g. Beautrais, 2002; Hawton and Harriss, 2006; De Leo et al., 2013; Jokinen et al., 2016). Chiu and colleagues (2004) found that almost one-third of older people in a Chinese community who died from suicide had a history of a suicide attempt, and that over 30% of these attempts had occurred within one week prior to the completed suicide. On the other hand, retrospective PA studies have indicated that nearly 75% of cases died on their first attempt (Chiu et al., 2004; Conwell et al., 2010), so effective public health strategies towards suicide prevention programmes must target both high-risk groups (e.g. those attempting suicide) and the general population, in accordance with Rose's theorem (Rose, 1985).

Both studies in the West (as summarized by Conwell et al., 2008) and the Orient (Chiu et al., 2004) indicate that, although the rate of psychiatric diagnosis is high, only a minority of decedents had consulted specialist psychiatrists before their fatal act. On the other hand, up to 80% had consulted a primary care doctor in the preceding month. In old age, depressive symptoms are often attenuated or expressed as physical symptoms and thus easily overlooked (Fountoulakis et al., 2003; Conwell and Thompson, 2008). These findings underscore the importance of screening for suicidal risk and depression, at the primary care level. A number of collaborative stepped-care management programmes targeting older primary care clients with chronic physical illness using algorithm-driven treatment of depression have shown that suicide ideation is sustainably reduced among the participants after completion of the programme, in addition to effective treatment of depression, for instance, the Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT) (Alexopoulos et al., 2005, 2009).

Several ecological studies have found an association between increased antidepressant prescription and fewer completed suicides based on national registry and population statistics, which points to the possibility that antidepressant use may be associated with a reduced risk for completed suicide at a population level (Henriksson and Isacson, 2006; Bramness et al., 2007). Such an association was also found in senior populations in Australia (Hall et al., 2003) and the UK (Shah and Lodhi, 2005), although causality is difficult to conclude in this type of study design.

Personality

Personality is a relatively under-researched domain in suicide studies among older people. Among the controlled studies, Harwood and colleagues (2001) reported that levels of anankastic (obsessional) and anxious traits significantly distinguished suicide from natural deaths, though personality disorder per se did not. Utilizing the NEO Personality

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Inventory (Costa and McCrae, 1992), Duberstein and colleagues (1994) found that of the five domains of personality measured (neuroticism, extraversion, openness to experience (OTE), agreeableness, and conscientiousness), high neuroticism and low OTE distinguished a group of individuals older than 50 years who completed suicide and an age- and gender-matched living comparison group. Low OTE was associated with reduced affective and hedonic responses, a reduced range of interests, and a strong preference for the familiar (Duberstein et al., 1994).

Both low OTE and the similar attribute of anankastic personality traits (as described by Harwood et al., 2001) might render older individuals more vulnerable to a negative impact from the challenges of ageing and thus an escalated risk for suicide when stressors arise. The findings on OTE and neuroticism were replicated in a study on Chinese older suicide attempters (Tsoh et al., 2005). In the same study, it was also found that, compared to community controls, suicide decedents were less extraverted, less agreeable, and less conscientious. Furthermore, when those completing and attempting suicide were compared, it was found that the former group was distinguished by their higher conscientiousness, agreeableness, and lower neuroticism. These attributes might contribute to a higher chance of people attempting suicide succeeding in their self-harm act, and/or might render their emotional distress less easily noticed by their relatives (Tsoh et al., 2005). Psychometric screening for early detection of impulsive behaviour and suicide proneness in susceptible groups of older people has been suggested to hold promise for shaping future prevention strategies (De Leo, 2002).

Physical health and functioning

Several case-controlled PA studies have examined the independent relation between common physical illnesses and suicide in older people. A study conducted in Sweden (Waern et al., 2002b) revealed that visual impairment, neurological disorders, and malignant disease were associated with elevated risk for suicide. A Canadian study also reported that chronic obstructive pulmonary disease (COPD), congestive heart failure, and seizure disorder were significantly associated with suicide in older people, and that their effect was cumulative (Juurlink et al., 2004). Studies conducted in Hong Kong (Chiu et al., 2004; Tsoh et al., 2005) found that COPD, arthritis, bone fracture, and malignancy were associated with completed suicide, and that stroke, bone fracture, arthritis, and malignancy were associated with attempted suicide. A population-based case-control study in the US found malignancy was independently predictive of completed suicide, especially in men (Cole et al., 2014). A ten-year prospective multisite study conducted in the US found that bone fractures were associated with suicide in older people (Turvey et al., 2002). Another 16-year longitudinal study performed in Australia showed that the predictive effects of major physical disorders were cumulative (Almeida et al., 2016). However, with the base rates of physical illnesses being very high in the older population, the usefulness

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in identifying individual older people who need intervention might be compromised (Conwell et al., 2011), with the possible exception of malignancies.

Conwell and colleagues (2010) also suggested that beyond individual physical illness, the perceived meaning of the illness burden and its impact on function, and limitations on autonomy and personal integrity, should not be overlooked. This is supported by case-controlled PA studies that showed that the presence of any impairment in instrumental activities of daily living (IADLs) was significantly associated with suicide case status (Conwell et al., 2010) and attempted suicide status (Tsoh et al., 2005) independent of the effects of physical and mental health disorders. Furthermore, a recent review of 45 studies from different nations that examined the relation between suicidal behaviours and functional impairment in middle-aged and older adults also confirmed the strong mutual associations (Lutz and Fiske, 2018).

Social factors

Social factors related to suicide in older people can be broadly classified into stressful life events, erosion of social support and connectedness (Conwell et al., 2011), perceived financial difficulties, and religious/spiritual factors.

Life events are often implicated as antecedents to suicide attempts and completed suicide in older people. Events related to physical illness, hospitalization, familial discord, interpersonal problems, retirement, bereavement, and social isolation are more typically associated with suicidal behaviour in later life (Heikkinen et al., 1995; Harwood et al., 2006). The association between stressful life events and completed suicide might be mediated through other risk factors for suicide, particularly depression. A case-control PA study in New Zealand (Beautrais, 2002) found that serious relationship and financial problems distinguished older people completing or attempting suicide from controls. The finding of a particular potency of familial discord has been replicated by other case-control PA studies in Sweden (Rubenowitz et al., 2001), the US (Conwell et al., 2010), and Hong Kong (Chiu et al., 2004; Tsoh et al., 2005).

Bereavement from the death of a spouse is a relatively common stressor in late life and is associated with elevated suicide risks after the acute event (e.g. Harwood et al., 2006; Ajdacic-Gross et al., 2008). On the other hand, widowhood per se is not uniformly identified to be a risk factor. A number of studies in Europe and Australia have found an increased suicide risk in widowers (Yip, 1998; De Leo et al., 2001; Corcoran et al., 2009); however, the reverse is true for older Chinese women in Hong Kong and Taiwan (Yip, 1998; Yip et al., 1998; Yeh et al., 2008). Furthermore, a study on all older suicide events between 1987 and 2005 in Switzerland found that, for both genders, the risk of suicide is elevated in the first week after bereavement; the risk then remains elevated for

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men but virtually vanishes after the first week for women (Ajdacic-Gross et al., 2008). These intriguing findings deserve further study. Stress arising from care given to a spouse with chronic illness has been consistently identified in studies from the US (Cohen et al., 1998; Karch and Nunn, 2011) and Australia (Milroy et al., 1997) in homicide-suicide cases. This is alarming, given the rapid rise of numbers of people with dementia due to population ageing.

Concerning social support, a case-control PA study conducted in New Zealand found that a low level of social interaction was an independent risk factor for suicide, after adjusting for physical and mental health variables (Beautrais, 2002). Similarly, a more recent case-control PA study in Australia reaffirmed that living alone was an important predictor of suicide in older adults (De Leo, et al., 2013). Furthermore, Turvey and colleagues (2002) found that an increase in the number of confidants was associated with a significantly reduced suicide risk in older adults.

The role of financial difficulties in older people's suicide is relatively under-researched. In PAs that have explored this factor, financial problems were present in around 13-19% of the suicide decedents (Heikkinen et al., 1994; Rubenowitz et al., 2001; Beautrais, 2002; Chiu et al., 2004; Tsoh et al., 2005). The results in controlled studies have been divergent. In the studies by Rubenowitz and colleagues (2001) and Beautrais (2002), monetary problems distinguished older people completing suicide from community controls, and Conwell and colleagues (2010) also found lower annual income (less than US \$35,000) distinguished the groups. However, such findings were not replicated in the controlled studies in Hong Kong (Chiu et al., 2004; Tsoh et al., 2005). Furthermore, in multivariate analyses, financial factors exerted no independent effect in the aforementioned studies by Rubenowitz and colleagues (2001) and Beautrais (2002), or in that of Conwell and colleagues (2010). It is therefore likely that the influence of this stressor is mediated through independent factors such as depression. However, generalization from these studies is limited by the particular socioeconomic contexts in which they were conducted (e.g. the variable extent of welfare provisions for retired individuals). Financial factors may also act at the societal level for instance, a study by Shah and colleagues (2008), found that among the 87 global nations studied, elderly dependency ratios (EDR) were positively correlated with older suicide rates. This is of concern, given the fast pace of worldwide population ageing, especially in developing countries where income protection for senior citizens is more likely to be limited.

Research studies examining the possible influence of religious and spiritual factors on suicide in older people are also sparse, despite their potentially profound roles in the maintenance of emotional health and coping with stress. In this domain, we should differentiate between studies that examine the salience of religion towards an individual (or 'religiousness') and those that have looked at the effect of affiliation to a specific religious denomination or particular set of spiritual beliefs. For

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the former, in a controlled study on persons aged 50 or over in the US, Nisbet and colleagues (2000) found that among 584 suicide cases, participation in religious activities was probably associated with a lower risk of completed suicide. The odds for having never participated in religious activities were greater among people dying by suicide compared with those dying from natural causes, even after adjustment for sex, race, marital status, age, and frequency of social contacts. In a controlled PA study and a controlled study on older suicide decedents and people attempting suicide in Hong Kong (Chiu et al., 2004; Tsoh et al., 2005), both studies found that those who considered religion as salient in their life had a fivefold reduction in the odds for suicidal behaviours. Pargament and colleagues (2001), Van Ness and Larson (2002), and June and colleagues (2009) have reported a generally protective effect of religiousness on mental health in older Americans, possibly by way of conferring stronger reasons for living, which generally help to counter suicidal behaviours. Furthermore, a recent meta-analysis of studies around the world concluded that the protective effect of religiosity against completed suicide is stronger in older populations (OR = 0.42, 95% CI: 0.21–0.84) (Wu et al., 2015).

Conwell and colleagues (2011) have postulated in a review article that religious and spiritual factors may be an important intrinsic constituent to the construct of social connectedness, and persons with low social connectedness are exposed to higher risk of self-destructive behaviours. However, there is also new evidence that religiousness might impart independent protective effects beyond general social connectedness (Rasic et al., 2009). Moral and religious objections to suicide are reported to be associated with less suicidal behaviour in people with depression, and are proposed to act as a protective factor against suicidal behaviour (Lizardi et al., 2008). This has been described specifically for populations with predominantly Islamic faith (e.g. Kok, 1988), so it is a surprising finding that, cross-nationally, there are significantly higher suicide rates in older men in Catholic countries compared to rates in other countries, with a trend for similar findings among women, despite the condemnation of suicidal acts attributed to Catholicism (Pritchard and Baldwin, 2000). Studies on negative religious coping or 'religious struggles' in older persons (e.g. those with thoughts of illnesses being signs of abandonment or punishment from God) might potentially illuminate this apparently paradoxical finding (e.g. Pargament et al., 2001).

On the other hand, in Oriental belief systems, delineation of religious denominations is much less clear-cut than the West. For instance, traditional Chinese religious beliefs have blended in heritages from Buddhism, Taoism, doctrines of Confucianism, regional folk religions, and ancestor worshipping (Cohen, 1992; Goossaert, 2005; Chamberlain, 2010). Moreover, collectively in traditional Chinese beliefs, ancestral spirits are commonly thought to dwell in a different world and as potentially imparting positive influences on filial descendants. Thus, during a perceived crisis, death may merely mean a different form of

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existence, or even an avenue to solve the many impasses in this life through reincarnation (Goodrich, 1991; Phillips et al., 1999). This could be a reason underlying the apparent weaker protective effect of religion against suicide in the Orient as compared to the West from the above-mentioned meta-analysis (Wu et al., 2015). Further studies in this area are obviously important, and hopefully methodological advances will help to disentangle these complex factors, leading to better interpretation of the data and application of the findings in evidence-based prevention programmes.

Other possible factors

Access to lethal means

Older adults are generally more ready to use more violent and potentially lethal methods for suicide attempts than younger age groups (Conwell et al., 2011). The prevalence of different methods of suicide varies with the availability of lethal means across different sociocultural contexts. For instance, the use of a firearm is the commonest method of suicide by older men in the US (Conwell and Thompson, 2008); in the UK, suicidal older men mostly die by hanging and women by drug poisoning (Cattell, 2000); in Hong Kong, the most common methods of suicide in older people are jumping from a height or hanging, while less violent methods (e.g. asphyxia from charcoal burning, an increasingly common method in Asian Pacific cities) are infrequent among older people (Chiu et al., 2004; Chan et al., 2009). In rural China, the commonest method in older people is ingestion of organophosphate pesticides or rat poisons, followed by hanging (Li et al., 2009).

Conwell and colleagues (2002b) found in a controlled PA study in the US that the presence of a firearm in the home was associated with a twofold increased risk for suicide, even after controlling for psychiatric illness. Measures to restrict access to lethal means have been demonstrated to have potential to lower overall suicide rates, especially where the method in question is readily available, with examples of success reported following coal gas detoxification in Switzerland and the UK, firearm restriction in Canada and Washington, DC, in the US (Mann et al., 2005), and legislations that limited the pack size of paracetamol and salicylates sold over the counter in the UK (Hawton et al., 2001).

In rural China, given the high rate of self-poisoning because of the easy availability of toxic substances (Li et al., 2009), the WHO has worked in recent years with Chinese governmental agencies to promote the use of safer products, as well as safer methods of storage (Chiu et al., 2012). There are now some pilot data showing that the use of 'boxes with a lock' for safe storage of pesticides in rural households is acceptable to the community in low-income countries (Konradsen et al., 2007), although further studies are necessary to examine the effectiveness of safe storage of pesticides in preventing suicide.

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Neurobiological theories

Several studies have reported that older people with depression who attempt suicide can be distinguished from controls without depression by their poorer executive functioning on neuropsychological profiling (King et al., 2000; Keilp et al., 2001; Dombrovski et al., 2008a,b). This could possibly translate into poorer problem-solving capabilities or a higher propensity for impulsive reactions in times of stress. In a community case-control study of adults aged 50 and over, clinical cerebrovascular risk factors were significantly higher among suicide decedents than among community-dwelling age- and gender-matched comparison participants, after adjusting for age, sex, depression diagnosis, and functional status (Chan et al., 2007). Similar findings were reported for older women attempting suicide in a controlled study in Hong Kong (Chan et al., 2014).

Reviews of neurotransmitter disturbances mostly point to possible age-related roles of the serotonergic, noradrenergic, and dopaminergic systems. For instance, in older people with depression, lower CSF levels of 5-HIAA were found in those who attempted suicide compared to those who had not (Conwell and Thompson, 2008).

To sum up, there are preliminary findings that late-life suicide is associated with disrupted neural substrates that might play crucial roles in impulse control, mood regulation, and cognition, and might represent important avenues for further understanding and prevention of self-harm behaviours in older people.

Protective factors

In contrast to the numerous studies on risk factors of suicide in older people, there is a relative paucity of studies on protective factors. The role of religious factors on suicide in older people has been examined earlier (see Social factors). Improving the social support to older people may be protective, as concluded in one study that found increased number of confidants associated with lower suicide risk in older people (Turvey et al., 2002). Two studies have attempted to improve resilience to modify suicidal behaviour risk. Lapierre and colleagues (2007) designed a programme for retired seniors based on a cognitive-behavioural approach. It consisted of an 11-week workshop and aimed to enhance meaning in the life of participants, and levels of depression, as well as suicidal ideas, were lower in the intervention group compared with the control group. The other study by Heisel and colleagues (2009) consisted of a 16-week interpersonal psychotherapy programme for older adults at increased risk of suicide to improve their social functioning so as to increase social support and satisfaction. There was a reduction of depressive symptoms and lower scores on the Geriatric Suicide Ideation Scale (Heisel and Flett, 2006) in the intervention group compared with the control group. Both of these studies are preliminary studies, but the results are encouraging.

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Prevention and intervention ('postvention')

Suicide prevention interventions are usually classified as: universal (targeting the entire population), selective (targeting symptomatic or pre-symptomatic individuals or subgroups who have distal risk factors for suicide, or who have a higher-than-average risk for developing mental disorders), or indicated (targeting individuals who have detectable symptoms or other proximal risk factors for suicide) (Conwell and Thompson, 2008). Examples of universal measures include restriction to the means for self-harm, promotion of healthy ageing, and de-stigmatization of mental illness. Improved access to rehabilitative care to promote functional independence in individuals with chronic medical conditions could be a selective measure for suicide prevention. Enhanced screening for depression, availability of effective treatment of this condition, and adequate follow-up of people attempting suicide ('postventions') are examples of indicated measures (Conwell and Thompson, 2008). A systematic review of suicide prevention strategies has found that the most promising interventions are physician education, means restriction, and gatekeeper education, while other methods (including public education, screening programmes, and media education) need more research (Mann et al., 2005).

To be effective, suicide prevention programmes must take into account the known barriers to suicide prevention, which include the following:

Older people completing suicide are more determined in their acts, plan their attempt with greater resolve, and display fewer external warnings of their intent compared to other age groups (Conwell and Thompson, 2008).

Older adults are less willing to communicate their suicidal intent compared with younger people (Scocco and De Leo, 2002).

The difficulty of timely identification of affective disturbances by non-psychiatrist physicians when older people present with multiple somatic complaints (e.g. Heikkinen and Lonnqvist, 1995).

The unwillingness of older people to seek specialist psychiatric care (and limited accessibility to such care in some nations), especially in the oldest-old population (aged 75 or over), despite the high rate of psychiatric morbidities in people who complete suicide. However, it should be borne in mind that most have seen a general practitioner in the month before their suicide act (e.g. Chiu et al., 2004; Conwell et al., 2011; Cheung et al., 2017; Szanto et al., 2001).

The therapeutic nihilism of some doctors towards older patients with depression (e.g. Uncapher and Arean, 2000).

Therefore, it has been recommended that effective and comprehensive prevention programmes should adopt a multicomponent approach, with a combination of universal, selective, and indicated interventions (Mann et al., 2005; Erlangsen et al., 2011).

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Recent large-scale suicide prevention strategies in older people have adopted multifaceted or multi-layered approaches, with particular attention to mental health. The Telehelp/Telecheck service operated in Padua, Italy, and provided telephone-based outreach, evaluation, and support services to older people who were isolated and functionally incapacitated. When assessed by De Leo and colleagues (2002) over a decade later, a reduction of suicide rates among women was identified. Oyama and colleagues reported that five to ten years after the launching of a programme in rural Japan that combined universal, selective, and indicated preventive interventions, the relative risk for suicide in older adults had dropped, with an especially significant reduction (64–76%) in the risk for suicide in older women (Oyama et al., 2005, 2006). Furthermore, in Hong Kong, the Elderly Suicide Prevention Programme (ESPP) was launched territory-wide in 2002. The initiative adopted a two-tiered, multifaceted, case-management model that offered prioritized and intensive treatment of depressed or suicidal older people referred from primary care providers or other medical disciplines over a period of at least six months. An evaluation study suggested that the programme was associated with a reduced suicide rate in women aged 85 and over in the population, relative to the pre-intervention period (Chan et al., 2011).

A systematic analysis of suicide prevention studies in older adults found that most of the described interventions aimed to reduce suicide risk factors, such as depression screening and treatment (Lapierre et al., 2011). Most studies found an effect on reducing suicidal thinking and the suicide rate in older adults, but the programmes showed most benefits in women. The authors suggested that strategies should aim to improve resilience, involve community gatekeepers, use telecommunications to contact vulnerable older adults, and evaluate the effects of means restriction and physician education on suicide in older people (Lapierre et al., 2011). A more recent systematic review of 21 available controlled intervention programmes around the globe to prevent suicidal behaviours and reduce suicidal ideation in older people revealed that there was supportive evidence for the effectiveness of multifaceted, collaborative primary care based depression screening and management programmes, treatment interventions with pharmacotherapy, telephone counselling for vulnerable older adults, and multi-levelled community-based programmes incorporating education, gatekeeper training, depression screening, group activities, and referral for treatment. Of these, findings were most robust for the collaborative primary care based program on reduction of suicide ideation in older adults. On the contrary, the evidences for programmes solely based on psychotherapies using cognitive behavioural therapies (CBT) were deemed inconclusive. A multi-level community intervention addressed known suicide risk factors in older persons and while the results on reduction of rates of completed suicides were favourable, all of these were hitherto conducted in the Far East and their generalizability would be limited by differences in cultures and healthcare systems (Okolie et al., 2017).

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Given the important contributory roles of physical illnesses and functional impairments towards suicide risk in older people, models that better integrate mental health care into the care pathways for general medical conditions should be further explored (Szanto et al., 2013; Okolie et al., 2017; Lutz and Fiske, 2018). Likewise, future suicide prevention programmes should also better address adequate social supports for older persons in need, considering the high rates of social disconnectedness among suicide decedents (Conwell, 2014; De Leo et al., 2013).

Conclusions

Suicide prevention initiatives in older people have taken a great stride forward in the past decade based on better understanding of the risk and protective factors pertaining to this great public health challenge. For further improvements to take place, sustained and determined collaborations across clinicians, researchers, health administrators, and policymakers are needed, given the complex, multi-determined nature of suicidal behaviours, a daunting task in many nations for various reasons (De Leo, 2002).

Moreover, it is important to note that older men are generally at higher risk of suicide than women: in many countries, they use more lethal means in their suicide acts, they are more susceptible to the effects of bereavement and widowhood, and they have responded less favourably to the most recent comprehensive suicide prevention programmes. Further research on the gender differences of suicidal behaviours is urgently needed, to understand the different underlying psychopathological mechanisms, and to adequately address the healthcare needs of older men, the largest contributing group to completed suicide instances across the world.

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Manic syndromes in old age

Chapter: Manic syndromes in old age

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Classification issues

Bipolar disorder (BD) is a chronic disease of abnormal mood and is characterized by episodes of either elevated mood or depression or, much less frequently, a mixed affective presentation of both elevated mood and depression. To satisfy a clinical diagnosis of BD there should be at least one hypomanic or manic episode, and the abnormal mood episodes (hypomanic/manic or depressed) should have a detrimental effect on the social and occupational functioning of the individual. Though the diagnostic criteria of this disorder are well demarcated in the younger adult population in both the ICD-10 and DSM-5 (WHO, 1992, American Psychiatric Association, 2013), the same cannot be said for BD in older people. The DSM-5 does not address age-related differences in presentation of BD. This may be because BD in older people is probably a heterogeneous illness, hence attempts to classify it remain controversial. In deference to this controversy, we choose the broader term of 'manic syndromes' in old age as the title of our chapter. We recognize that

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recently there are reasons to believe that it can be broadly divided into two main groups: the patients with late-onset bipolar disorder (LOB) and those with early-onset bipolar disorder (EOB), and we describe these in more detail later. Perhaps the most important evidence concerning differences between younger adult and older bipolar patients comes from genetic studies. Although bipolarity is strongly influenced by genetic factors in the younger adult population (Goodwin, 1990), there is less evidence of such a relationship in the geriatric population. In this chapter, we elaborate on differences between mania in younger adults and older people, between LOB and EOB, discuss aetiopathological findings, and offer suggestions for management.

Shakespeare (through Juliet) asks 'What's in a name? That which we call a rose by any other name would smell as sweet'. While it is true that reality matters, not the name used to denote it, the opposite is not the case; using the same name for different things does matter (Vasudev and Thomas, 2010). Since older people with LOB disorder seem to have a different symptom profile with a different epidemiology and different aetiologies compared with younger people, it appears 'bipolar disorder' may not be an appropriate name for this symptom constellation in older people.

Epidemiology and clinical presentation

There is evidence suggesting that the age of the patient as well as the age of onset of the disorder are two different variables that require consideration for a better understanding of the epidemiology of the illness.

Prevalence

Bipolar illness usually affects people by the age of 30 and it has been estimated that 90% of cases are younger than 50 years of age when they have their first episode (Hirschfeld et al., 2003). This implies that 10% of bipolar patients will develop their illness after the age of 50, and a study by Kennedy and colleagues (2005) did find that around 10% of a population sample had a first incidence of mania after the age of 60. In a more recent review of the literature, Dols and colleagues (2014) estimated that six patients out of every 100 admitted to a psychogeriatric unit were manic, and of those six, two to three were likely experiencing their first manic episode, irrespective of previous depressive episodes.

Data from epidemiological studies suggest that BD in the general adult population has a prevalence rate of around 1% in the community (Regier et al., 1993). This may be an underestimate. Evidence is accumulating that BD and schizophrenia illnesses are two ends of a spectrum and often there is an overlap of symptoms and progression (Laursen et al., 2009). Indeed, if screening tools like the Mood Disorder Questionnaire (MDQ) are used for estimation of prevalence, 4% of the population might be

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considered to have had a lifetime episode of hypomanic or manic symptoms (Hirschfeld et al., 2003).

In contrast, the prevalence and incidence rate of mania in old age in the community is not very well established. This is because methodological factors confound the data. Some of the concerns are inherent in identifying individuals with mania in the community as they are not readily amenable to interview or cooperation with surveys. Furthermore, the literature is limited by data drawing upon cross-sectional retrospective analyses, under-representing secondary mania due to somatic illness or medications, and deriving primarily from specialist centres, thus limiting generalizability to the community (Dols et al., 2014).

Epidemiological studies conducted in the older population in the community using strict diagnostic criteria have found prevalence rates varying from 0.08% to 0.25%. Other prevalence studies also suggest that the figure for lifetime prevalence of BD in older people in the community is around 0.1% (Weissman et al., 1988; Unutzer et al., 1998; Hirschfeld et al., 2003). The reasons for differences in prevalence rate between the general adult population (around 1%) and that in older people (as low as 0.1%) remains a matter of controversy and no epidemiological factors are obvious for the discrepancy. Some suggest the influence of a relatively high mortality rate from natural causes and from suicide, as well as evidence for 'burn out' of the disorder over a long-term course (Winokur, 1975; Snowden, 1991). These studies were, though retrospective in nature, reflecting the difficulty in following up patients with BD over their lifespan. More recent expert consensus, however, suggests a prevalence (conservatively estimated at 0.5–1% of older adults) approaching that observed in the younger population, as reported by the International Society for Bipolar Disorder (ISBD) Task Force on Older-Age Bipolar Disorder (OABD) (Sajatovic et al., 2015b).

In selected populations such as nursing homes (9.7%; Koenig and Blazer, 1992) and inpatients (varying from 8 to 10%; Depp and Jeste, 2004; a prevalence of 6% was found in a more recent review including 1,519 inpatients older than 50; Dols et al., 2014), there are significantly higher prevalence rates. The higher prevalence in such populations perhaps is a reflection of the course of the illness; when older individuals suffering from BD have an affective relapse they need higher levels of care and cannot be managed in the community.

Also, until recently, it was believed that BD had a bimodal frequency distribution with a peak of episodes in early adulthood and another peak in late life (Cassidy and Carroll, 2002; Kessing, 2006). However, this view has been challenged as data also suggest a unimodal frequency distribution with no such peak later in life (Almeida and Fenner, 2002; Kennedy et al., 2005).

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Age at onset

Epidemiological data are better defined in late-life BD with regards to the age of onset of the illness. It is thought that this variable helps distinguish the subtypes of mania and hence lead to an improved understanding of pathogenesis and aetiology (Young and Klerman, 1992; Leboyer et al., 2005). The older person with BD may be considered to be of two types (see Fig. 41.1). The first group may be referred to as LOB, with the first episode of the affective disorder occurring late in their life; most studies consider this to be greater than 50 years of age. The other group is EOB, who when older are 'graduates' with the disorder, having had the onset of the illness at a younger age (less than 50 years of age). The demarcation is useful as clinically these two groups are different.

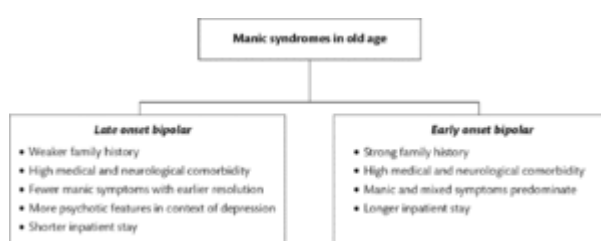


Fig. 41.1

Conceptual framework for differentiating manic syndromes in old age based on age of onset of bipolar disorder.

It should be noted that, while the traditional consensus cut off age for LOB has been 50 years or greater, the first report of the ISBD Task Force on OABD proposes that some consideration be given to reducing the cut-off age to 40 years in order to provide a broader lifespan perspective (Sajatovic et al., 2015b).

It has been argued that EOBs have a high familial rate of BD, while LOBs do not show this pattern consistently (Depp and Jeste, 2004). Others find a similar rate of family history between LOB and EOB (Motes et al., 2013). The estimated rates of familial penetrance in the older group per se vary between 24% and 88% (Glasser and Rabins, 1984; Shulman et al., 1992; Hays et al., 1998). The reason for this variation could be related to methodological issues such as the rigor of investigation and the criteria used for a positive family history of BD (e.g. whether only first-degree relatives are considered). Within the older group, it has been estimated that there is twice the familial penetrance rate in the EOB group compared to the LOB group (Stone, 1989; Hays et al., 1998). In an elegant review of the literature, Azorin and colleagues (2012) summarize the diverse conceptualizations of LOB, including LOB as a 'secondary' disorder to organic illness (especially right hemisphere lesions), as an expression of attenuated genetic vulnerability, and as 'Bipolar Type VI', the last of which follows Akiskal's spectrum concept of bipolar illness, with type VI representing a syndrome of mixed-labile-agitated episodes in

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the setting of dementia. It may be that a family history of any psychiatric illness is more prevalent in EOB, such as affective disorders, psychotic disorder, or substance abuse (Leboyer et al., 2005). In such cases and in addition to the genetic loading that comes with a family history of illness, the emotional distress of having an affected parent or other close family member could contribute to the triggering of an earlier onset (Thesing et al., 2015).

Clinical presentation and age of onset

There are no consistent differences between the clinical presentation in the young patient with BD versus the older patient, or between older patients with EOB versus LOB (Sajatovic et al., 2015b; Depp et al., 2004). This is not to say that differences in phenomenology have not been found, but findings across studies are not reliably present. For instance, using a cut-off point of 49 years, one study found the LOB group of older patients to have more psychotic features and more cerebrovascular risk factors (Wylie et al., 1999), whereas another study described more nuance in older patients, noting that the older cohort was more likely to have psychotic features as part of a depressive, as opposed to a manic, episode (Kessing, 2006). LOB patients have also been described to have fewer and milder manic symptoms compared to the EOB or the young manic patient and a tendency to have irritable mood rather than elated mood (Sajatovic, 2002). Further support for the idea of milder symptomatology comes from The National Network of Depression Centres Clinical Care Registry, in which later-life bipolar patients were found to have fewer and less severe depressive symptoms (Forester et al., 2015). In a recent longitudinal study comparing the outcome of LOB and EOB patients followed up after a manic or a mixed affective relapse, it was reported that LOB patients had a quicker remission of their illness and a greater proportion were discharged from an inpatient facility (Oostervink et al., 2009).

In terms of disease characteristics, older bipolar patients (EOB and LOB considered together) seem to have a larger time gap between a depressive episode and a manic one. In a prospective study (Jeremy and Robin, 1990), the mean time between the first episode of depression and the onset of mania was 17 years in the older group versus three years in the younger group. This study also found that, compared to their younger peers, older patients were more likely to have suffered three or more depressive episodes before their first manic episode. This result is not entirely concordant with the finding in another study, in which patients with LOB had significantly less of a delay from the time of symptom onset to a BD diagnosis (3.3 years) than patients who present earlier in age (18.6 years) (Montes et al., 2013), possibly due to a shorter time period from depression to onset of mania.

Interestingly, the older manic patient appears to be more likely to relapse into depression after mania. The older bipolar patients (>60, irrespective of age of onset) in the 24-month follow up of the large, prospective observational study, European Mania in Bipolar Longitudinal Evaluation

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of Medication (EMBLEM), also were significantly more depressed than the younger (<50) cohort, as measured by the Clinical Global Impression-Bipolar (CGI-BP) scale (Oostervink et al., 2015). The EMBLEM group also reported a greater proportion (40%) of older patients had a recurrence of an acute mood episode relative to the younger group (23%) over the course of the study. Furthermore, the older patients had a shorter time to recurrence (544.6 days versus 593.5 days), with recurrence defined as a relapse following remission. These results suggested to the EMBLEM group that, while remission may be easier to achieve in older patients, recovery is harder to maintain, possibly reflecting a higher cycle frequency in older patients. However, the two age groups did not differ significantly with respect to rates or time to remission and recovery. No difference was found between older EOB (first manic episode at age younger than 50 years) and LOB patients on any measure of recurrence or relapse, although a greater number of older LOB patients tended to achieve recovery (defined as functional recovery) than their peers of the same age group but with an early onset pattern of illness.

Some of these findings indicate that older people with BD have a different clinical pattern, involving more depression and possibly milder manic symptomatology, especially in the LOB group. This could be a reflection of differences in comorbidity, which we discuss next.

Comorbidities

Comorbidities may include psychiatric and physical disorders. BD in adult outpatients is often comorbid with various psychiatric conditions, formerly identified as axis I conditions, including lifetime and current substance use, anxiety, and eating disorders (McElroy et al., 2001). However, large-scale epidemiological studies such as this have tended to include younger adults as well as older people in the same group; in only *some* studies has subgroup analysis been attempted (for example, Kodesh et al., 2012). In a review of the literature, Lala and Sajatovic (2012) identified seven small cross-sectional or retrospective studies with bipolar patients older than 50, and found the most common concurrent diagnoses were anxiety and substance use disorders, albeit at a lower rate and with lower severity than in the younger cohort. Cassidy and colleagues (2001) found a lifetime substance abuse rate of around 29% in a subgroup of older bipolar patients. This contrasted with a substance abuse rate of around 48% in the younger adult bipolar population. Interestingly, the older bipolar patient tended to have more hospital admissions compared to the younger bipolar patient. In a more recent study, Goldstein and colleagues (2006) found the one-year prevalence rate in late-life BD highest for alcohol abuse (38.1%), followed by panic attack (11.9%), generalized anxiety disorder (9.5%), and dysthymia (7.1%). In a Spanish multicentre study of elderly outpatients with BD, Montes and colleagues (2013) reported current alcohol use disorder and tobacco use disorder as 15.9% and 11.6%, respectively.

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There are fewer data on the prevalence of personality disorders (formerly axis II conditions) in late-life BD. In a study on outpatients as well as inpatient populations of late-life affective disorders, 63% had a personality disorder based on their responses to a structured interview for personality. There was no difference in the prevalence rate between the depressed and the bipolar group (Molinari and Marmion, 1995). This is similar to a lifetime odds ratio of having an axis II diagnosis of 10.6 (95% CI 9.2–12.3) (equivalent to a percentage prevalence of 53% by imputation assuming 5% prevalence in the adult population) in the general adult bipolar population in a large community survey (Grant et al., 2005).

There are few large prospective and case-controlled investigations into medical comorbidities across the lifespan of bipolar patients. Data from the younger adult demographic suggests that, relative to healthy controls, bipolar adults have an increased risk of the following: early onset of cardiovascular disease (Goldstein et al., 2015; Hays et al., 1998); cerebrovascular disease (Subramaniam et al., 2007); diabetes mellitus, hypertension, cancer (Kodesh et al., 2012); neurological conditions (Shulman et al., 1992); overall burden of medical illness (Soreca et al., 2008); obesity (Goldstein et al., 2013); and premature mortality from general medical conditions (Roshanaei-Moghaddam and Katon, 2009). Whether this extends into old age is not firmly established, although some data appears to suggest that elderly bipolar patients are no more afflicted with illness than the general elderly population (Tsai et al., 2009; Gildengers et al., 2008a). This may reflect a ‘survivor effect’ in which EOB patients who graduate into old age represent a healthier subgroup relative to their cohort of a similar age of onset who may have died prior to reaching a geriatric age (Leboyer et al., 2012). An alternative explanation may include the bipolar elderly receiving more fragmented or inconsistent primary care, leading them to be potentially underrepresented in these studies (Rise et al., 2016).

One small Taiwanese study compared 59 euthymic bipolar I patients sixty years or older with age and education matched healthy individuals, and found that bipolar patients in their study had significantly *less* hypertension and lower mean systolic blood pressures than their non-bipolar counterparts (Tsai et al., 2009). Furthermore, the Taiwanese bipolar sample did not have greater estimates of cardiovascular morbidity relative to the general elderly population, despite having higher rates of diabetes. On average, elderly bipolar patients were found to have three to four comorbid medical conditions (Lala and Sajatovich, 2012). Research from the Bipolar Disorder Centre for Pennsylvanians Study has attempted to estimate other medical illness burden in patients with late-life BD (Gildengers et al., 2008). They found that patients 60 years of age or older with late-life bipolar had similar total medical morbidity, as measured by the Cumulative Illness Rating Scale-Geriatrics (CIRS-G), as age-matched unipolar depressed patients. Those with BD had a higher BMI and increased burden of endocrine/metabolic and respiratory disease

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as measured by the CIRS-G sub-scores. Because CIRS-G scores in late-life depression are increased compared with non-psychiatric controls, this study suggests the same is true for late-life BD, although direct comparisons are needed (Baldwin, 2008).

In a cross-sectional study of chronic non-cancer pain (for example: back pain, arthritis, chronic pain, migraines, neuropathic pain) in American veterans, bipolar patients, including over 58,200 aged 50 or above, were found to have a significantly greater likelihood of having any pain condition (OR = 1.85) than patients with schizophrenia (OR = 0.91), but significant less likelihood than patients with major depression (OR=2.3) (Birgenheir et al., 2013), which is an interesting finding that parallels the view that BD exists in the middle on a continuum between schizophrenia and unipolar depression.

Inflammation may be the mechanism by which the bidirectional relationship between psychiatric and medical illness is explained, and understanding BD as a multi-system inflammatory disease is gaining momentum as an explanatory model (see Leboyer et al., 2012; Sajatovic et al., 2013). Alternatively, longstanding lifestyle variables such as sedentary lifestyle, tobacco use, poor diet high in saturated fats, and obesity undoubtedly contribute to medical comorbidity in BD, as they do in any serious and persistent mental illness (Compton et al., 2006; Ward et al., 2015; Scott and Happell, 2011). To address whether medication use may be a factor in medical comorbidity as measured by rates of medical hospitalization, a large Canadian cohort study compared acute medical or surgical admissions to hospitals in late-life bipolar patients receiving lithium only, valproate only, or neither lithium nor valproate over one year following psychiatric hospitalization. (Rej et al., 2015). Interestingly, there was no significant difference between any of the groups in terms of time to medical hospitalization, reasons for acute medical hospitalization, medical outcomes, or medical comorbidity rates.

With regards to physical illness, a number of studies have shown an increased prevalence of neurological illnesses, as defined variously, but especially including dementia and cerebrovascular disease in patients with LOB (Depp and Jeste, 2004, Subramaniam et al., 2007, Shulman et al., 1992). A large longitudinal study confirmed that the elderly bipolar patient has double the odds of developing stroke compared to age matched controls over a period of six years (Lin et al., 2007), which appeared similar to findings in unipolar disorder (Thomas et al., 2004), although once cardiovascular risk factors were controlled for, this increased risk in BD became negligible in a study involving younger adult bipolar patients (Prieto et al., 2016).

In a similar vein, the context of poststroke mania, or 'secondary mania' as described in psychiatric literature, tends to be like the concept of 'disinhibition syndrome' as preferred by neurologists. Perhaps this reflects the same pathology but is labelled differently by different group of clinicians. It is now relatively well established that normal mood is

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dependent on the integrity of the frontal, limbic, and basal ganglia circuitry. To understand the pathology observed in secondary mania, the relevant neuroanatomical domains are as follows: frontal lobes modulate motivational and psychomotor behaviour; limbic connections modulate emotions; while the biogenic amine nuclei in the hypothalamus, amygdala, and brainstem modulate instinctive behaviours. It is therefore understandable that any loss in these neural circuits can lead to mania (Starkstein and Robinson, 1997). In addition, several case reports suggest that the right part of the cerebral cortex seems to be more affected in patients with secondary mania (Braun et al., 1999). Other authors also consistently argue that right-sided cerebral lesions subsequent to head injuries or other causes of organic brain damage lead to a 'disinhibition syndrome', similar to what is found in 'secondary mania' (Starkstein et al., 1990; Strakowski et al., 1994; Verdoux and Bourgeois, 1995; Steffens and Krishnan, 1998). The role of the cerebellum as an important structure in post-stroke mania is also evident from cases of posterior circulation infarction (Das et al., 2015).

Cognitive impairment is often found in younger patients with BD even in the euthymic stage (Martinez-Aran et al., 2004). Years of education and age at last manic/hypomanic episode were shown in one study to be important predictors of cognitive impairment, followed by age at first depressive episode and presence of a manic episode prior to the age of 40 (Tsai et al., 2007). This impairment continues into older age (Dhingra and Rabins, 1991), and seems to cause global, generalized deficits (Mann-Wrobel et al., 2011; Gildengers et al., 2013; Aprahamian et al., 2014), as highlighted by one study in which more than half of euthymic older bipolar patients scored one or more standard deviations below the mean of age- and education-matched comparison subjects on cognitive screening instruments, the MMSE, and the Mattis Dementia Rating Scale (Gildengers et al., 2004). Some researchers have found that particular cognitive domains are preferentially affected, although findings are not consistent between studies (for example, verbal learning and memory, Kurtz and Gerraty, 2009; processing speed and episodic memory, Delaloye et al., 2011; executive function and verbal memory, Robinson et al., 2006). In a study of a middle-aged and older population, bipolar patients underperformed comparably to patients with schizophrenia in tests involving reasoning/problem solving, and visual memory/learning, but performed marginally but significantly better on tasks involving other skills. These same BD patients had worse performance across domains with a much larger effect size compared to mentally healthy subjects, leading to a tentative conclusion that the neurocognitive impairments in BD more closely approximate those in schizophrenia, albeit with subtle and small differences (Depp et al., 2004). In comparing deficits between bipolar I, bipolar II, and unipolar patients in the acutely depressed phase, one group of researchers observed impairment in the same four domains (processing speed, memory, verbal fluency and executive function), albeit with greater severity in the bipolar I group (Xu et al., 2012).

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Whether there is a progressive component to the cognitive impairment seen in BD is still a matter of debate. Some studies (see, for example, Sanamé et al., 2013; Robinson and Ferrier, 2006) find stability over time with older bipolar patients having an equivalently impaired neurocognitive profile relative to the younger patients, suggesting that impairment occurs early but is stable over time, or at most parallels the cognitive changes that occur in normal ageing, as suggested by the findings in one five year follow-up study (Schouws et al., 2016). The findings from other studies, however, observed more pronounced deficits in the older group (Depp et al., 2007), out of keeping with age and education (Gildengers et al., 2009). In support of the latter view, two separate 24-month prospective studies did not find an accelerated course of cognitive decline between euthymic bipolar patients and normal cognitive subjects (Gildengers et al., 2013; Delaloye et al., 2011). This fits in with theory of 'neuroprogression', which posits that impairments are illness- and not age-dependent (Goodwin et al., 2008; Cardoso et al., 2015), implying that structural rewiring of brain networks occurs as a result of repeated mood episodes. This observation aligns itself well with findings in the unipolar depression literature in which late life depression is associated with more cognitive impairment than that observed earlier in the course of illness, and which continues even when controlling for the effect of ageing (Thomas et al., 2009). Certainly, one study has found more severe cognitive impairment in LOB patients compared to elderly EOB, although the confounder in this study is that the EOB group was on average four years younger than the LOB group (Schouws et al., 2009),

Taken together, this might suggest that several older bipolar patients have cognitive deficits similar to and in the range of mild cognitive impairment (MCI), the latter often being regarded as the precursor state to dementia. This hypothesis has not been well investigated, as most studies compare cognition in bipolar patients to control subjects judged to have 'normal' cognition. In fact, it is possible the cognitive deficits in patients with BD are different from those who have MCI, as suggested by a recent study in which the cognitive deficits in older adults with Bd (mean age 63 years) were compared to those with MCI and no history of affective disorder. Patients with MCI were more impaired in verbal memory, whereas BD patients showed more deficits in attention, calculation, and verbal abstraction (Silva et al., 2009).

Whether there is a link between dementia and BD as exists between the former and late-life depression (Ownby et al., 2006; Gualtieri and Johnson, 2008; Brommelhoff et al., 2009; Himmelhoch et al., 1980) does not appear to have been settled. Some authors have commented on the difficulty in differentiating between behavioural symptoms associated with Alzheimer's disease (AD) and LOB (example, Depp and Jeste, 2004; Ng et al., 2008), and in recognition of that, one group has attempted to develop a computer-aided diagnosis system using clinical observation, neuropsychological testing, and inflammatory and neurotrophic biomarkers to discriminate between the two disease entities (Besga et al.,

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2015). Further evidence that BD and AD can be distinguished biochemically came from a study in which the signature AD CSF profile of low amyloid-beta peptide levels and high concentration of hyperphosphorylated tau protein was not found in patients with late-life BD (Forlenza et al, 2016), suggesting that cognitive impairment in LOB is not via the pathological mechanisms present in AD. In a small neuroimaging study, this lack of common pathophysiology is indirectly supported by the finding that late-life bipolar patients had a smaller burden of white matter hyperintensities (WMH) than healthy comparators, despite having more cognitive impairment (Rej et al., 2014a), which is not in keeping with emerging consensus that WMH is a preclinical and independent biomarker for AD (Lee et al., 2016; Mortamais et al., 2014).

There is interest in the use of lithium to potentially preserve cognitive function in BD. Rybakowski and colleagues (2009) found a beneficial effect of lithium prophylaxis on executive cognitive function. There have also been interesting results from a large ten-year follow-up study (1995–2005) conducted in Denmark (Kessing et al., 2008). Two groups were compared: 16,238 persons who had purchased lithium at least once in the community (implying a possible diagnosis of BD) and 1,487,177 persons from the general population who had not purchased lithium. Patients who purchased lithium at least once had an increased rate of dementia compared with persons not exposed to lithium (relative risk, 1.47; 95% CI, 1.22–1.76), providing further evidence that BD increases the risk of dementia. For persons who continued to take lithium, the rate of dementia decreased to the same level as the rate for the general population, suggesting a protective effect of lithium. More disappointing is that another small study (Gildengers et al., 2008b) found that twelve older adults with BD who were prescribed donepezil for 12 weeks showed no improvement in either ADL score or cognitive test scores at the time of completion of the study.

These findings suggest that late-life BD patients are, at minimum, at increased risk of cognitive impairment, and possibly dementia. There are some data on a possible protective effect of lithium for preventing dementia, but good-quality intervention studies are needed to investigate this and to determine if better control of vascular risk factors improves outcome.

Prognosis

Suicide has been consistently shown to be one of the important causes of mortality in patients with affective disorders, especially in patients younger than age 35 after an interval of seven to 12 years of illness (Tsai et al, 2002). Whether this risk continues into older age, irrespective of early or late onset, is unclear. In their comprehensive review of the literature, Depp and Jeste (2004) did not find increased rates of suicide in elderly patients with BD, offering the possible interpretation that, in the case of EOB, elderly patients represented a ‘survivor cohort’. In a large

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longitudinal study of patients suffering from affective disorder admitted to an inpatient unit who were followed up for more than 34 years, it was observed that those patients who were on psychotropics (including antidepressants, neuroleptics, and lithium) had significantly reduced completed suicide rates compared to those not treated (Angst et al., 2002). Indeed, in a retrospective analysis of cases of older bipolar patients who had a suicide attempt, usage of antidepressants and mood stabilizers was noted to have reduced suicide attempt rates compared to age- and sex-matched controls (Aizenberg et al., 2006).

There is a relative paucity of research in how older patients with BD fare in terms of psychosocial functioning. There appears to be an additive effect of ageing and disease on older patients with BD manifesting in reduced quality of life, impacted cognitive skills, and ability to perform physical tasks (Weisenbach et al., 2014). Extrapolation from prospective data in the younger population in which one year psychosocial functioning in patients with multiple mood episodes is found to be significantly lower than in those with a history of only a single episode (Rosa et al., 2012) supports the concept of sustained impairment, possibly due to the progressive neurotoxicity of repeated episodes (Gildengers et al., 2013). In the Taiwanese study cited earlier, elderly patients with BD had a mean General Assessment of Functioning (GAF) score and Community Psychiatrist Rating Scale (CPRS) score significantly below their non-bipolar counterparts (Tsai et al., 2009). In a study of middle-aged and elderly adults with BD (ages 45–85 years), bipolar patients were found to have comparable scores on Quality of Well-Being scale and Medical Outcome Study-Short Form Health Survey (SF-36) relative to age-matched schizophrenia patients, and substantially lower scores relative to older healthy comparators (Depp et al., 2006).

Aetiopathology

Analogous to the vascular depression hypothesis in late life, the hypothesis that mania in late life may have a vascular cause has generated much interest (Wijeratne and Malhi, 2007). In a study of patients with late-life BD, a higher Framingham Stroke Risk Score was found in LOB versus EOB (Subramaniam et al., 2007). Huang and colleagues (2012) found imaging evidence of silent cerebral infarctions in over half of elderly bipolar patients irrespective of age of onset. Also, in a sample of older bipolar patients (n=119), more vascular risk factors predicted poorer cognitive performance (Schouws et al., 2010). Cerebrovascular disease is also reflected in the extent of brain WMHs as revealed by neuroimaging. The seminal paper proposing the relationship between LOB and cerebrovascular illness was described over twenty years ago with the description of a significantly higher incidence of silent cerebral infarcts in late onset mania relative to earlier onset as demonstrated by WMH on magnetic resonance imaging (MRI; Fujikawa et al., 1995). There are consistent findings of an increase in WMH in patients with BD (Lloyd et al., 2009) and even more so in LOB (Tamashiro et al., 2008); the latter of these found that there were more WMH in the

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deep frontal and parietal lobes and the putamen in LOB patients compared to age-matched older people with EOB, findings that correlated well with a similar study of mood disorders more broadly in which late-onset patients with an affective disorder had more deep WMH than age-matched early onset subjects (Takahashi et al., 2008). There is evidence that in unipolar disorder in older people, WMH are due to hypoxia-ischaemia (Thomas et al., 2002), but there have been no studies in BD. The aetiology of WMH may be a result of deficits in vascular perfusion (Thomas et al., 2002).

Though it is relatively well established that traumatic brain injury in the younger adult population can cause secondary mania as a neuropsychiatric sequel, the evidence for this association in older people is much weaker. There are only a few case reports of secondary mania in this population because of either anoxic encephalopathy (Ku et al., 2006) or thalamic damage (Lopez et al., 2009). Although it seems reasonable that brain injury would have similar or worse effects in older people, good studies are needed to demonstrate this.

Brain volume changes

There is increasing characterization of the neural substrates of late-life BD, made possible with advances in neuroimaging techniques such as structural MRI to estimate brain volume. There are contradictory reports of the extent of brain volume changes in late-life BD, with some research indicating no difference in gray matter and white matter volumes between euthymic older adults and healthy comparators (Delaloye et al., 2011; Sarnicola et al., 2009) whereas other researchers have found a significant volumetric difference between euthymic BD patients age-matched and gender-matched controls. This has obvious implications for the question of whether there is an active neurodegenerative process at play in BD, and certainly progressive gray matter loss has been documented in the longitudinal studies of the non-geriatric bipolar population (Moorhead et al., 2007). On balance, it appears that evidence is accumulating for there being focal areas of more specific atrophy in later age BD (Brambilla et al., 2001), where smaller gray matter volumes have been shown bilaterally in the inferior frontal areas (Beyer et al., 2009), along with decreased right caudate volume (Beyer et al., 2004a), smaller left hippocampal (Beyer et al., 2004b), and right posterior cingulate gyrus (Huang et al., 2011) volumes, and age-related reduction of amygdala volume (Doty et al., 2008). Interestingly, there is some evidence of an *increase* of volume in specific areas in middle-aged patients with BD (Jones et al., 2009), which may reflect compensatory neuroplasticity and is of particular importance given its cortical and subcortical connections with other brain areas controlling emotions and mood, as well as its role in regulating memory.

Unfortunately, there is little research on whether LOB has a different neuroimaging pattern from EOB (Hahn et al., 2014). One study has found *smaller* posterior cingulate gyri and *larger* left caudate nuclei and left

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middle frontal gyri in late-onset mania patients relative to the age-matched early-onset mania group (Huang et al., 2011). These authors hypothesized that the smaller cingulate gyrus may be due to the protective effect of medications taken earlier in life or could reflect the higher burden of cerebrovascular disease in the late-onset mania group. They further ventured that the left caudate nucleus and middle frontal gyrus may be relevant to the pathophysiology of early onset mania, with the implication being that these structures in the late-onset mania group were in fact more representative of normal.

Recent findings of reduced brain derived neurotrophic factor (BDNF) in older patients with BD (Soares et al., 2016) is particularly compelling in the context of this evidence of selectively reduced brain volumes in BD as BDNF is known to be critical for neurogenesis and neuroplasticity, raising the question of whether BDNF may be a mechanism between prolonged affective illness and dementia, as has been proposed in major depressive disorder (Kim et al., 2016).

Brain connectivity

It is recognized that bipolar patients have impaired connectivity between different areas of the brain because of disruption to the connecting white matter tracts (Benedetti and Bollettini, 2014; Bellani and Brambilla, 2011). Diffusion tensor imaging (DTI) is a relatively new neuroimaging technique that allows measurement of water diffusion within the neural tissue, which in turn provides information about white matter integrity. Abnormal DTI is thought to indicate damage to axonal membranes, demyelination, or reduced axonal density and thickness. Interest in the use of DTI as a means of exploring functional differences between healthy brains and those of bipolar patients is gaining momentum, as reflected by the number of papers published over the past decade. However, as noted by Nortje and colleagues (2013), the attempts to summarise the literature are inconsistent. For example, one meta-analysis of ten studies of DTI in BD suggested two significant clusters of decreased connectivity in right subcortical regions (areas close to the posterior parahippocampal gyrus, to the right anterior and subgenual cingulate cortex, respectively) (Vederine et al., 2011), whereas another review identified more evidence for loss of white matter network connectivity involving the prefrontal and frontal regions with less consistent and robust evidence for subcortical and non-frontal lobe areas (Heng, Song, and Sim, 2010). Yet another meta-analysis identified a right posterior temporoparietal and two left cingulate area as significant clusters of white matter alterations (Nortje et al., 2013).

Further complicating the application of the literature to late-life BD is the fact that the current research focus is primarily on the adult populations and information on microstructural white matter changes in late-life BD may have to be extrapolated from the adult data. In the only published study (Haller et al., 2011) in older bipolar (LOB and EOB together) patients conducted on only 19 patients, there was significantly decreased

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connectivity in the ventral part of the corpus callosum. This was supported by a report by Sexton and colleagues (2012) that there was abnormal connectivity as measured by DTI within the corpus callosum of 10 LOB patients compared to unipolar patients and healthy volunteers, supporting the hypothesis that abnormal interhemispheric connectivity is a feature of the disorder. It is still unclear to what end the use of DTI in the study of late life BD will be helpful, but it may ultimately be shown to be a neurobiological marker to help distinguish late life bipolar from other nosological entities, such as unipolar depression and AD (Teipel et al, 2014; Besga et al, 2016).

Inflammation/oxidative stress

An exciting development in our understanding of the aetiopathology of BD generally is the mounting evidence that chronic inflammation may be present in even the earliest stages of disease (Goldstein et al., 2009). Whether inflammation plays a distinct role in late-life BD is understudied, but interestingly the interleukin-1 (IL-1) family of cytokines, but not other inflammatory cytokines, were found to be elevated in euthymic bipolar older patients with cognitive impairment, increasing the speculation that IL-1 may be involved in impaired cognitive functioning in BD (Lotrich et al, 2014). Increases in the acute-phase reactant C-reactive protein also appears to be associated with BD, and independent of medication use (Dargel et al., 2015). Inflammation may play a role in the induction of increased markers of oxidative stress that have been found in older BP patients. For example, higher peripheral levels of lipid hydroperoxide, a surrogate measure of oxidative damage, were found in 110 euthymic patients older than 50 compared them to 75 age-matched healthy comparators (Andreazza et al., 2015). These findings supported a previous study from the same group in which elevated LPH levels were associated with WM abnormalities in the prefrontal cortex in euthymic adult bipolar patients, with the inference being that lipid peroxidases target the axonal membranes and myelin sheaths of WM tracts (Versace et al, 2014).

These findings show that our knowledge of the aetiopathology of late-life BD is limited, but the best evidence so far supports a role of cerebrovascular disease.

Management

This section focuses on those features of the management of BD that are distinct for older people. Most fundamental, given the high prevalence of neurological morbidity in late-life BD, is the need to search assiduously for localizing neurological signs and symptoms. A careful history, being alert to evidence of head injury, cerebrovascular disease, and related risk factors, is essential in light of our current understanding of the illness. Indeed, neuroimaging may be considered as an important component of the investigation of the older manic patient, especially LOB (van Gerpen et al., 1999). Furthermore, given our understanding of the probable role

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cerebrovascular risk factors play in the aetiopathology of LLB, both primary and secondary preventive strategies at the level of general medical care of these risk factors become important (Compton et al., 2006; Leboyer and Kupfer, 2010; Ward et al., 2015).

The ISBD Task Force for OABD is drawing increasing attention to the lack of specific recommendations for the management of the older individual with BD in the various international and national treatment guidelines (Dols et al., 2016). In general, combined medication treatment (for example, a mood stabilizer and an anti-psychotic) for late-life BD is the rule, rather than the exception (Oostervink et al., 2015). In a retrospective study on patterns of pharmacotherapy and treatment response following up 138 acutely unwell patients in a single centre, it was observed that mood stabilizers were the most prescribed (68%), followed by antipsychotics (54%), and antidepressants (34%). Combination therapy with these medications was more common than monotherapy (57% vs 38%). Remission was achieved in only 35% of subjects, while 32% showed no significant improvement (Beyer et al., 2008). A recent multisite, cross-sectional naturalistic study in the US found greater rates of antidepressant prescription in late-life bipolar patients, defined in this study as patients 55 years and older. These findings suggested to the authors that older adults may respond more efficaciously to antidepressants, although they cautioned that the population reported fewer and less severe depressive symptoms, suggesting that a prospective study was required to establish cause and effect (Forester et al., 2015). In a multisite cross-sectional study, elderly EOB patients were found to be receiving a higher mean number of psychotropic medications (3.3) relative to elderly LOB patients (2.3), as well as higher antidepressant use (71.7% relative to 35.3%) and higher mean daily dose of antipsychotics (257.3 mg of chlorpromazine equivalent relative to 175.54 mg) (Montes et al., 2013).

Results from the multicentre prospective EMBLEM study have been of interest. At a 12-week outcome point, a total of 2,761 patients had been treated for a manic episode, including 475 over the age of 60 (Oostervink et al., 2009). At that juncture, it was found that LOB patients (n=141) tended to be maintained on typical antipsychotics, lithium, and anticholinergics, much more than EOB patients (n=323), and that after an episode of manic or mixed affective relapse there was an increase in prescription of atypical antipsychotics and a consequent decrease in typical antipsychotic use. Rapid cycling older patients had a higher use of antidepressants (40%) compared to non-rapid cycling older patients. The EMBLEM data also suggested that, while older bipolar patients as a group differed from younger patients in terms of treatment, treatment outcomes in the short term did not differ between the age groups. A further analysis of patients over 60 did suggest that treatment outcome was more favourable for the LOB patients than for the EOB when assessing on the physician-rated CGI scale.

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At the 24-month follow up, greater use of antidepressants in older (relative to younger) patients was observed, as well as less frequent use of atypical antipsychotics, and greater use of other concomitant psychiatric medications, such as anticholinergics, benzodiazepines and other hypnotics. Prescribing rates of anticonvulsants and lithium did not differ relative to younger bipolar patient. No statistically significant differences in prescribing was found between older EOB or LOB patients, although the authors acknowledge that the small numbers in these subgroups could reflect a type 2 error, thus preventing the detection of a clinically relevant difference (Oostervink et al., 2015). Unlike what was found at the 12-week time point, after two years no statistically significant differences in treatment outcome could be found between EOB and LOB patients.

Of note, the evidence base for psychotherapeutic treatments in the younger bipolar patient group is relatively strong, with different approaches being effective in different phases of the illness. Family therapy, interpersonal therapy, and systematic care appear to be effective in preventing recurrences when initiated after an acute episode, whereas cognitive behavioural therapy and group psychoeducation appear to be most effective when initiated during a period of recovery (Miklowitz, 2008). However, there has been less investigation of the effectiveness of nonpharmacological treatments of late-life BD. While there are some encouraging findings from psychosocial intervention trials (Fagiolini et al., 2009), no randomized controlled trials (RCTs) have been reported hence we do not offer any specific recommendations for such treatment approaches.

As a general therapeutic approach, one needs to be aware that pharmacological treatment of any disorder in older patients is challenging because of pharmacokinetic and pharmacodynamic changes associated with ageing, as well as an increased risk of drug interactions (see Chapter 13). In view of these challenges, one needs to be cognizant of the risk of such interactions. In a ward-based study of older aged psychiatry patients found that 96% of prescriptions had a potential for drug-drug interactions, with an average of eight drugs prescribed for each patient (Vasudev and Harrison, 2008).

Mood stabilizers

Lithium

Lithium continues to be a commonly used mood stabilizer in old age. Traditionally some clinicians and patients have been reluctant to use lithium as first-line treatment because of concerns regarding frequent blood level monitoring, nephrotoxicity, and the narrow therapeutic window. A recent cross-sectional study, however, has demonstrated that patients using lithium for BD (n=46, mean age 68.7) actually report higher contentedness, somatic health, and social functioning than counterparts using anticonvulsants or other medications (n=30, mean

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age 68.1) (Rej et al., 2016). This attitude holds true despite higher rates of adverse effects (polyuria, thirst, tremor, and fatigue being reported in 48 lithium users). In addition, the BALANCE trial, a pragmatic RCT in working-age adults, has revisited lithium again and concluded that, for adults with bipolar I disorder for whom long-term therapy is clinically indicated, both combination therapy with lithium plus valproate and lithium monotherapy are more likely to prevent relapse than is valproate monotherapy (Geddes et al., 2010). Unfortunately, there are still no RCTs on the use of this agent in the pharmacological treatment of older bipolar patients. There are, however, several open-label trials and retrospective reports that suggest that even older, frail patients can be safely and effectively treated (Himmelhoch et al., 1980; Shulman and Post, 1980; Chen et al., 1999; Fahy and Lawlor, 2001; Gildengers et al., 2005). Furthermore, there is evidence that age is not a determinant of erratic serum lithium levels (van Melick et al., 2013).

Evidence suggests lithium may help in reducing progression to dementia in late-life BD (Nunes et al., 2007; Kessing et al., 2008; Dell'Osso et al., 2016), findings that may improve clinicians' favourability towards the use of lithium in older people. Long-term lithium may be related to better white matter integrity, as demonstrated by a small study comparing the MRI of older BD patients with a mean lithium exposure of 13.8 years to an otherwise similar group of BD patients with either no or less than one year of lithium treatment (Gildengers et al., 2015). While this preliminary study is very interesting and supports the hypothesis that lithium may be neuroprotective, this same study did not demonstrate an association between duration of lithium exposure and global cognitive functioning. Interestingly, in a cross-sectional rank order analysis of the relative neurocognitive effects of psychotropic medications, lithium ranked behind lamotrigine and oxcarbazepine in terms of cognitive favourability, but ahead of carbamazepine, valproic acid, and topiramate (Gaultieri and Johnson, 2006), which may reflect lithium's known serum anticholinergic activity (Chew et al., 2008). At this time, it is difficult to reconcile the cognitive blunting effects of which patients on lithium often complain with the concept of lithium's neuroprotective role. Another factor to consider is the increase in sensitivity to lithium by age. Adverse reactions and toxicity levels have been reported in older people even with serum levels within the 'safe' and therapeutic range (Roose et al., 1979; Murray et al., 1983). However, under well-controlled conditions in a specialized geriatric clinic, lithium is reported to be safe and well tolerated (Parker, 1994).

Lithium must be used with caution in the geriatric population as it is eliminated exclusively by the kidneys and may be excreted in older people at a rate approximately half that of younger patients (Hardy et al., 1997). This has led to the recommendation that in old age, only half the adult dose should be prescribed. Lithium use appears to be safe in geriatric patients who have normal kidney function (Rej et al., 2015); caution needs to be exercised in patients where the baseline estimated

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glomerular filtration rate (eGFR) is less than 60 ml/min/1.73 m² (stage three chronic kidney disease) and in such patients adverse renal outcomes are more likely (Rej et al., 2014b). Unfortunately, this applies to a large proportion of older people. The traditional wisdom about the inexorable nephrotoxicity of long-term lithium therapy is being revised in light of a recent large population-based cohort study in which the rate of change in eGFR over 12 years of lithium-treated adult patients was comparable to patients on quetiapine, olanzapine, and valproate (Clos et al., 2015). This should not, however, prevent a cautious prescriber from remaining alert to potential lithium nephrotoxicity, especially in an older patient with other medical comorbidities, or to seek alternative treatments in patients with baseline renal disease. Lithium has been known to cause nephrogenic diabetes insipidus through various mechanisms, including alterations in purinergic signalling (Zhang et al., 2009), disturbance in epithelial sodium channel functioning in the collecting ducts (Kortenoeven et al., 2009), and dysregulation of renal aquaporins and acid-base transporters (Nielsen et al., 2008). Perhaps in the future, newer treatments will be available to counteract the effects of lithium on the kidneys, but at the moment no specific recommendations are available for the management of lithium-induced nephrotoxicity, although amiloride has been found to be beneficial to some extent (Bedford et al., 2008). Prudence would suggest that the clinical management of such a patient should be done collaboratively with a nephrologist.

Additionally, lithium can cause a wide range of systemic adverse reactions, including those on the central nervous system. Lithium induces tremors, aggravates parkinsonian tremor, and causes spontaneous extrapyramidal symptoms. Interestingly, one Canadian study showed that chronic lithium use is associated with the prescribing of Parkinson medications such as levodopa, prompting the authors of this study to speculate that this prescribing cascade made be the inappropriate treatment of lithium-induced action tremor (Marras et al., 2016). One community study found that almost a third of older patients on lithium were on thyroid replacement or else had elevated levels of thyroid stimulating hormone (Head and Denning, 1998), and another study of 1,705 new lithium users over 65 years of age found it treated hypothyroidism in almost 6% of the sample, twice the prevalence expected among a mixed-age population (Shulman et al., 2005b). Lithium can also cause frank encephalopathy when taken as an overdose or when combined with various neuroleptics. Cautious slow withdrawal is usually found to alleviate the symptoms (Swartz and Dolinar, 1995; Boora et al., 2008).

Drug interactions continue to be an ongoing concern with lithium, particularly when thiazide diuretics are prescribed as these can significantly lower lithium clearance and thereby put the patient at risk of toxicity by increasing the serum lithium levels. Other medications of concern include the angiotensin-converting enzyme (ACE) inhibitors and

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non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin. In an observational study of 10,615 older lithium users, 3.9% had been admitted to hospital for lithium toxicity. In this study, initiation of a loop diuretic like furosemide or an ACE inhibitor significantly increased the risk of lithium toxicity, while neither thiazide diuretics nor NSAIDs were independent risk factors (Juurlink et al., 2004).

Anticonvulsants

Valproic acid, lamotrigine, and carbamazepine are standard medications in the treatment of BD in the adult population. While they have proven efficacy as mood stabilizers, one must remain mindful of their exhaustive list of serious drug interactions, and concerns for their safe and well-tolerated use in an older population in whom frailty and comorbidities are more often the rule rather than the exception. Moreover, there is limited data on anticonvulsant use in older bipolar populations and a paucity of specific guidelines for their use. There are some important class effects of which to be mindful in the older population, such as sedation (Mula and Trimble, 2009), reduced bone mineral density and increased fracture risk (Lee et al., 2010), and memory impairment (Montamendi and Meador, 2004), although the latter may be more of a concern for the older generation anticonvulsants (valproic acid, carbamazepine) than lamotrigine (Mula and Trimble, 2009).

Valproic acid or its congener, divalproex, are now frequently used in the treatment of BD in the younger adult population. Some evidence suggests that valproate therapy is now used more frequently for older bipolar patients than even lithium (Shulman et al., 2003; Sajatovic et al., 2004). There are no RCT data available, but there are a number of published case reports and case series (Risinger et al., 1994; Gildengers et al., 2005). These studies indicate that valproate is an effective and well-tolerated mood stabilizer in the older population, although in this population it is important to remain mindful of the finding that valproate had the most neurocognitive effects of the anticonvulsants after carbamazepine (Gaultieri et al., 2006). Though there are recommendations that valproate should be up-titrated quickly for acute management of mania in the adult population, there are no such recommendations in the older population. This is possibly because of the higher incidence of adverse effects even at therapeutic dosages. Principal side effects include sedation and gastrointestinal disturbance, which can be modulated by dosage reduction (Shulman and Herrmann, 1999). Indeed, valproate did not fare better than lithium in a relatively large study comparing differences in hospitalization rate for delirium in 2,422 lithium users compared to 2,918 valproate users (Shulman et al., 2005a). Use of valproate is associated with a relatively high incidence of thrombocytopenia, an often under-recognized side effect of this medication, which may occur frequently in older people (Trannel et al., 2001). There are several case reports of valproic-acid induced parkinsonism (Mahmoud and Tampi, 2011) and hyperammonaemic encephalopathy (Mittal et al., 2009), which suggests caution while

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prescribing. There also may be merit in using valproate in the treatment of rapid cycling illness in old age (Gnam and Flint, 1993), though as there are no RCTs, one must be cautious in extrapolating results to the routine clinic.

Valproate is highly protein bound. There is a risk of higher adverse events when consumed at higher dosages, which may be related to higher total as well as unbound drug levels in the blood. This may result from complex protein binding. It has been shown that the protein binding of valproate decreases as the serum concentration increases (Felix et al., 2003). The drug is also a moderate broad spectrum inhibitor the CYP system and UGT-glucuronidation (Fenn et al., 2006), which leads to the potential for multiple drug interactions with non-psychiatric medications commonly prescribed to the older adults, such as warfarin and acetylsalicylic acid (Virani et al, 2012; Fenn et al, 2006). Furthermore, co-administration of valproic acid and psychotropic medications can be tricky; for instance, valproate has been found to inhibit the metabolism of tricyclic antidepressants and displace diazepam from protein binding sites, thus increasing their plasma concentrations (Janicak, 1993).

Carbamazepine, a mood stabilizer preferred in the past, is still recommended in various guidelines for the management of BD in younger adults. The British Association for Psychopharmacology recommends that it could be used for acute mania that is mild in severity and for prevention of relapse in bipolar I patients (Goodwin, 2009). Its clinical usage in the geriatric population is low, perhaps because of its risk of drug interactions, auto-induction, rash, and high neurotoxicity. It has the potential to cause hyponatraemia, an imbalance that is always poorly tolerated in the elderly and which can present as a confusional state (Fenn et al., 2006). Therapeutic target serum levels might be a bit lower for the geriatric population and some authors suggest keeping serum levels below 9 µg/ml (Young, 1996), although carbamazepine is notorious for its wide interindividual variation in pharmacokinetics.

Among other mood stabilizers, gabapentin has been found to be beneficial in some case reports. Two case series used gabapentin in a subsample of older patients (Ghaemi et al., 1998; Cabras et al., 1999). There is some evidence of lamotrigine's efficacy in BD in those greater than 55 years of age (Marcotte, 2004). In an open-label trial of treatment of refractory BD, a number of older patients appeared to tolerate lamotrigine (Calabrese et al., 1999). In a subanalysis of older subjects enrolled in a placebo-controlled trial of maintenance therapy for bipolar I disorder, 33 patients were treated with lamotrigine (Sajatovic et al., 2005), and it was found that lamotrigine was significantly better than placebo at delaying time to intervention for any mood disorder. The average age of these older subjects was, however, only 62. A multisite, open-label, prospective trial of lamotrigine (mean dose 150.9 mg/day) for geriatric bipolar depression found nearly 60% remission and response rate in the study population of type I and II bipolar depression (n=57, mean age 66 years) (Sajatovic et al., 2011). Dropout rates due to adverse events were modest (10.5%), and

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included rash (four patients), manic switch (one patient), and hyponatraemia (one patient). A number of side-effects were noted including both reduced and increased sleep, weight loss and weight gain, increased dreams, polyuria, diminished sexual desire, fatigue, and unsteady gait.

Among other anticonvulsants there was some early evidence for levetiracetam (Kyomen, 2006), although a more recent review of RCTs emphasizes that mood stabilization is not a class effect for anticonvulsants (Rosa et al., 2011), and levetiracetam specifically has no efficacy as a mood stabilizer (Dubovsky et al., 2015).

Antidepressants

Antidepressants have a role in the acute treatment of a depressive episode in unipolar depressive disorder in older people as well as prophylaxis in preventing relapse. For the treatment of BD, monotherapy with antidepressants has also been linked to an increased risk of a manic episode, also called as 'switching' (Goodwin, 2009). Additionally, a bigger concern is that antidepressants may not offer any clinical benefit per se. A recent systematic review and meta-analysis of use of antidepressants in adult BD highlighted that antidepressants do not offer clinical superiority over placebo for treatment response or remission (Sidor, 2011). Additionally, we found no good-quality studies exploring the use of antidepressants in late-life BD and hence we do not elaborate much on their usage.

Antipsychotics

Some antipsychotics have displayed efficacy in late-life BD, especially as medications useful in the management of acute mania. For instance, in a post hoc analysis of noncontrolled data, Sajatovic and colleagues (2008a) found quetiapine monotherapy to be effective for the acute treatment of bipolar mania in adults greater than 55 years of age, and in an open-label trial, this group showed evidence for efficacy of aripiprazole in a small (n=20) study of older adults in acute mania (Sajatovic et al., 2008b). Similarly, 88 depressed old age bipolar patients were randomized to lurasidone monotherapy, and after six weeks, the average improvement in Montgomery-Asberg Depression Rating scale was significantly greater for lurasidone monotherapy relative to placebo, with an impressive effect size of 0.83 (Sajatovic et al., 2016). Further work is needed on the use of this agent especially since adjunctive lurasidone therapy did not demonstrate efficacy.

Asenapine has been approved by the Federal Drug Administration for adult use in acute and mixed mania as either monotherapy or as an adjunct to lithium or valproate, and has been found to be efficacious and well tolerated. In the 2013 guideline updates for Canadian Network for Mood and Anxiety Treatments (CANMAT) for the management of BD, asenapine is included as a new first-line monotherapy option for the treatment of acute mania (Yatham et al., 2013). In a small open-label

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study in Tel-Aviv, 11 admitted psychogeriatric (mean age 67.7) patients with acute bipolar mania were treated with a mean daily dose of 20 mg of asenapine (Baruch et al., 2013). Treatment was discontinued in two patients, for rash and severe peripheral oedema, respectively, with complete resolution in days following medication discontinuation. Improvement in Young Mania Rating Scale (YMRS) was significant at day 28, with improvement noted in all the YMRS items. For the nine patients that remained on asenapine for four weeks, all achieved response (defined as a $\geq 50\%$ decrease in YMRS total score from baseline), and all but two attaining remission (YMRS total score ≤ 12). Overall, asenapine was well tolerated with only mild sedation reported by minority of the patients. Similar findings of tolerability and efficaciousness were found in a small (n=15, mean age 68.8) open-label trial in which community-dwelling seniors exhibiting diminished functional abilities, or lability, irritability, or agitation due to BD were tried on asenapine at an average dose of 11.2 mg daily after suboptimal control on their current medication (Sajatovic et al., 2015a). Maintenance medications for BD were continued provided no changes had been made in the previous 30 days. One patient was lost to follow-up and three dropped out prematurely because of perceived medication side effects, one of whom developed a mixed manic state. Of the 11 who completed the 12-week trial, there was significant improvement in scores for the Brief Psychiatric Rating Scale, and the CGI bipolar version scale. Tolerable side effects that did not lead to study discontinuation included gastrointestinal distress, restlessness, tremors, cognitive difficulties, and sluggishness/sedation.

Management of cognitive impairment

As for the pharmacological management of cognitive impairment in BD, the data is limited and of inferior quality (Sanches et al., 2015). Cholinesterase inhibitors have been tried but with mixed results, suggesting that the nature of cognitive impairment at the neurotransmitter level involves something other than cholinergic deficits. In a small, open label trial of donepezil 5–10 mg in older patients with late life BD and minor cognitive decrements, Gildengers and colleagues (2008b) observed no significant effects in cognitive or functional measures after three months. Overall, the research into pharmacological management of cognitive impairment of late-life BD is in its infancy.

Conclusion

Late-life BD, especially LOB disorder, appears to be a different entity from BD in the younger population. Late-life BD is frequently associated with vascular changes in the brain and these may be of aetiological significance. There is also cognitive impairment associated with late-life BD and there is some evidence that lithium might prevent further deterioration in cognition. Good quality RCTs of psychotropics in both acute and maintenance stages are needed, as currently practice is based

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largely on extrapolation of clinical evidence from younger bipolar patients, who may have a different kind of illness.

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Anxiety disorders in older people

Chapter: Anxiety disorders in older people

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Introduction

Fear and anxiety are phylogenetically ancient emotions that confer survival advantage across species (Darwin, 1872). They facilitate escape from present danger and prepare the individual to deal rapidly with future threats. In contemporary life, a moderate increase in anxiety is commonly associated with increased performance (Yerkes and Dodson, 1908). However, anxiety that is excessive or prolonged is maladaptive and may represent a mental disorder. Individual differences and contextual factors influence the final form that an anxiety disorder takes. Like many complex behaviours, anxiety disorders result from interactions between genetic and environmental factors. In older people, anxiety often complicates physical frailty and cognitive decline. From a nosological perspective, anxiety can be conceptualized as both dimensional and categorical. Both psychological and pharmacological treatments are commonly applied to anxiety disorders in older people, with moderate efficacy. This chapter deals with classification, epidemiology, scientific

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underpinnings, phenomenology, and modern treatment approaches to anxiety disorders in later life.

Classification

The tenth edition of the International Classification of Diseases (ICD-10) includes anxiety disorders, including obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) within a broad category of neurotic, stress-related, and somatoform disorders (World Health Organization, 2010). In contrast, DSM-5 has a section for anxiety disorders and separate sections for OCD and PTSD (American Psychiatric Association, 2013). Similar changes have been made in ICD-11, with data reporting from participating countries to commence in 2022 (World Health Organization, 2018). For ease of reference we retain OCD and PTSD in this chapter. Table 42.1 shows the classification of anxiety disorders under ICD-10, ICD-11, and DSM-5. There is considerable commonality between the lists of anxiety disorders under the two dominant nosologies, reflecting convergence over time. ICD-10 is currently under revision, with ICD-11 due in 2018. The most significant change to the diagnostic criteria for anxiety disorders introduced in DSM-5 was the deletion of DSM-IV PTSD criterion A2, which required the person to have experienced 'intense fear, helplessness or horror' at the time of the traumatic exposure (Friedman et al., 2011). In ICD-11 (World Health Organization, 2018), complex post-traumatic stress disorder (6B41) has been added to the nosology and acute stress disorder relegated from a disorder to a problem (acute stress reaction, QE84).

Table 42.1 Anxiety disorder classifications.

ICD-10	ICD-11	DSM-5
F40.0 Agoraphobia, unspecified	6B02 Agoraphobia	300.22 Agoraphobia
F40.01 Agoraphobia with panic disorder		
F40.02 Agoraphobia without panic disorder		
F40.10 Social phobia	6B04 Social anxiety disorder	300.23 Social anxiety disorder (social phobia)

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F40.2 Specific phobia	6B03 Specific phobia	300.29 Specific phobia
F41.0 Panic disorder	6B01 Panic disorder	300.01 Panic disorder
F41.1 Generalized anxiety disorder	6B00 Generalized anxiety disorder	300.02 Generalized anxiety disorder
F41.2 Mixed anxiety and depressive disorder	6A73 Mixed depressive and anxiety disorder	<i>No corresponding disorder in DSM-5</i>
F41.3 Other mixed anxiety disorders	<i>No corresponding disorder in ICD-11</i>	<i>No corresponding disorder in DSM-5</i>
F42 Obsessive-compulsive disorder	6B20 Obsessive-compulsive disorder ^a	300.3 Obsessive-compulsive disorder ^b
F43.0 Acute stress disorder	<i>No corresponding disorder in ICD-11, but QE84 Acute stress reaction (not a disorder) can be coded</i>	308.3 Acute stress disorder ^d
F43.1 Post-traumatic stress disorder	6B40 Post-traumatic stress disorder ^c	309.81 Post-traumatic stress disorder ^d
F43.22 Adjustment disorder with anxiety	6B43 Adjustment disorder	309.24 Adjustment disorder with anxiety ^d
F43.23 Adjustment disorder with mixed anxiety and depressed mood		309.28 Adjustment disorder with mixed anxiety and depressed mood ^d
F06.4 Anxiety disorder due to a known physiological condition	6E63 Secondary anxiety syndrome	293.84 Anxiety disorder due to another medical condition

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Various disorders listed under F10-F19	Various disorders listed under 6C40.71-6C4G.71	292.8 Substance/medication-induced anxiety disorder
F41.8 Other specified anxiety disorders	6B0Y Other specified or fear-related disorders	300.09 Other specified anxiety disorder
F41.9 Anxiety disorder, unspecified	6B0Z Anxiety or fear-related disorders, unspecified	300.00 Unspecified anxiety disorder

^aIn ICD-11, Obsessive-Compulsive Disorder has been moved into a separate chapter: Obsessive-Compulsive or Related Disorders.

^bIn DSM-5 Obsessive-Compulsive Disorder has been moved into a separate chapter: Obsessive-Compulsive and Related Disorders.

^cIn ICD-11 Post-traumatic Stress Disorder and Adjustment Disorder have been moved into a separate chapter: Disorders specifically associated with Stress.

^dIn DSM-5 Acute Stress Disorder, Post-Traumatic Stress Disorder, and the Adjustment Disorders have been moved into a separate chapter: Trauma- and Stressor-Related Disorders. Source: data from Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5, 2013, American Psychiatric Association; data from International statistical classification of diseases and related health problems, 10th Revision, 2010, World Health Organization.

Epidemiology

There is now a substantial literature on the prevalence of anxiety disorders in older people, although a firm consensus is yet to emerge due to unresolved substantive and methodological issues. Bryant and colleagues (2008) have reviewed anxiety disorder prevalence estimates and associated methodological issues. Most population-based surveys find that the prevalence rates for anxiety disorders fall significantly after the age of about 50 years. The reasons for this oft-repeated observation are unclear. The observation that this effect begins in middle age makes it particularly challenging to explain using conventional age-related arguments. It has been suggested that the diagnostic interviews used to detect anxiety disorders are not appropriate for use in older people (O'Connor, 2006; O'Connor and Parslow, 2010), or that the diagnostic criteria themselves have intrinsic age biases. Using data from 1,738 self-reported worriers, Hobbs and colleagues (2014) investigated whether age influences the probability of endorsing GAD criteria and thus the prevalence of GAD. They found that respondents aged 60 years and over

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were less likely than younger adults to endorse most of the GAD criteria. Although non-invariance of the GAD criteria was present, this had only a small impact on the prevalence of GAD. They argued that this finding supported the validity of age-related declines in GAD prevalence. Anxiety disorder prevalence rates are higher in women than men at all ages, including later life. However, there is some evidence that the sex difference in anxiety prevalence might decline in advanced old age (Pachana et al., 2012).

Table 42.2 provides a summary of non-hierarchical 12-month population prevalence estimates for anxiety disorders according to DSM-IV and ICD-10 criteria in persons aged 65–85 years and in persons aged 16–64 years, based on the 2007 Australian National Survey of Mental Health and Wellbeing (NSMHWB) (Australian Bureau of Statistics, 2007). This population survey employed trained lay interviewers, who used the Composite International Diagnostic Interview (CIDI). The survey included 1,905 community-residing persons aged 65 years and over, but it did not sample persons residing in hospitals, nursing homes, or caravan parks. The two diagnostic systems generated somewhat different prevalence estimates for panic disorder, agoraphobia, and PTSD, with ICD-10 providing higher estimates in each case. The survey did not measure the prevalence of simple phobia. The population prevalence estimates in Table 42.2 are associated with relatively wide confidence intervals (CI), indicating the level of imprecision with which the estimates were made. The variations in prevalence estimates between the DSM-IV and ICD-10 nosological systems can be explained by differences in their diagnostic criteria. To illustrate this, let us take panic disorder as an example. Both DSM-IV and ICD-10 require a person with panic disorder to experience multiple, unexpected panic attacks, and the definitions of a panic attack are similar under each system. The main difference is that ICD-10 requires the person simply to experience recurrent panic attacks (World Health Organization, 2010), whereas DSM-IV requires the person to experience recurrent panic attacks and one or more sequelae, including a persistent concern about having another attack, worry about the implications or consequences of the attack, or a significant change in behaviour following the attack (American Psychiatric Association, 2000). Thus, in NSMHWB, similar proportions of older people reported having experienced panic attacks in the past 12 months under the DSM-IV and ICD-10 criteria, but the absence in ICD-10 of the requirement for one or more panic attack sequelae meant that the prevalence of panic disorder was much higher under this system than when the DSM-IV criteria were applied (see Table 42.2). So, these different prevalence estimates do not reflect minor methodological issues, but major differences in the way disorders are conceptualized or formalized. These differences might need to be taken into consideration when basing service development or funding decisions on epidemiological data.

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Table 42.2 Twelve-month prevalence rates for DSM-V and ICD-10 anxiety disorders.

	DSM-V 12-month prevalence (95% CI)		ICD-10 12-month prevalence (95% CI)	
	65-85 years	16-64 years	65-85 years	16-64 years
Generalized Anxiety Disorder	1.4 (0.8-1.9)	4.3 (3.8-4.7)	1.5 (1.0-2.1)	3.7 (3.3-4.1)
Panic disorder	0.5 (0.2-0.9)	2.2 (1.9-2.6)	0.9 (0.5-1.4)	3.1 (2.7-3.5)
Agoraphobia (+/- panic disorder)	0.3 (0.1-0.6)	1.6 (1.3-1.9)	1.0 (0.6-1.5)	3.4 (3.0-3.9)
Social phobia	1.2 (0.7-1.7)	5.4 (4.8-5.9)	1.3 (0.8-1.8)	5.8 (5.3-6.4)
Post-traumatic stress disorder	1.6 (1.1-2.2)	5.3 (4.8-5.8)	2.5 (1.8-3.2)	7.9 (7.3-8.6)
Obsessive-compulsive disorder	0.7 (0.4-1.1)	3.1 (2.7-3.5)	0.7 (0.4-1.1)	2.4 (2.0-2.7)
Any anxiety disorder	4.3 (3.3-5.2)	14.2 (13.4-15.0)	6.0 (4.9-7.1)	17.1 (16.1-17.9)

These population-weighted estimates were calculated from the confidentialized unit record file of the National Survey of Mental Health and Wellbeing, Australian Bureau of Statistics (2007). All diagnoses are non-hierarchical. Source: data from Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5, 2013, American Psychiatric Association; data from International statistical classification of diseases and related health problems, 10th Revision, 2010, World Health Organization.

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One method of attempting to sort out the validity of competing diagnostic approaches in a clinically meaningful way is to measure the degree of distress and disability associated with a diagnosis. Using the 12-item Short Form Health Survey (SF-12) to gauge disability, Slade and Andrews (2001) have shown in adults 18 years and over that DSM-IV GAD is associated with greater disability than ICD-10 GAD.

The Longitudinal Ageing Study Amsterdam (LASA) used a two-stage design to investigate the consequences of anxiety disorder and anxiety symptoms in people aged 55–85 years (de Beurs et al., 1999). The anxiety disorders studied were panic disorder, GAD, OCD, and phobic disorders. Older people with an anxiety disorder, or with anxiety symptoms, reported worse perceived health, greater loneliness, worse life satisfaction, and greater health services utilization than age-matched controls (de Beurs et al., 1999). In a US study of people aged 60–80 years who were seeking treatment for GAD and a matched control group, Wetherell and colleagues (2004) analysed quality of life using the 36-item Short Form Health Survey (SF-36). In this study, GAD was associated with worse health-related quality of life across almost all SF-36 domains and these associations were present regardless of whether GAD was complicated by comorbid psychiatric disorder. In addition, Porensky and colleagues (2009) demonstrated that older people with DSM-IV GAD have higher disability, worse health-related quality of life, and greater healthcare utilization than matched comparison participants without GAD.

The MentDis_ICF65+ study estimated the 12-month prevalence of anxiety disorders in people aged 65 to 84 years in five European countries and Israel (Canuto et al., 2018). The overall prevalence of any anxiety disorder adjusted for site, gender and age was 17.2% (95% CI: 14.0–20.4). The prevalence of any anxiety disorder was significantly greater in women (23.5%; 95% CI: 20.5–26.6) than in men (9.5%; 95% CI: 8.1–11.0) ($p < 0.001$). There was a significant linear downward trend in prevalence with age ($p < 0.001$). The prevalence of the individual anxiety disorders was as follows: panic disorder 3.8% (95% CI: 2.6–5.0), agoraphobia 4.9% (95% CI: 3.3–6.6), social phobia 1.3% (95% CI: 0.6–2.1), generalized anxiety disorder 3.1% (95% CI: 1.9–4.3), post-traumatic stress disorder 1.4% (95% CI: 0.4–2.4), and obsessive-compulsive disorder 0.8% (95% CI: 0.3–1.4). Of the individual anxiety disorders, agoraphobia and generalized anxiety disorder occurred more commonly in women.

The *incidence* of anxiety disorders in older people has been less well studied. However, using data from Wave 2 of the US National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) based on the Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV), Chou et al. (2011) estimated the weighted three-year incidence of non-hierarchical DSM-IV anxiety disorders in 8,012 persons aged 60 years and over as follows: GAD 1.63%; specific phobia 1.35%; panic disorder 0.76%; and social phobia 0.58%. Incidence estimates for other anxiety disorders were not reported. Participants

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aged 80 years and over were at greater risk of incident panic disorder than participants aged 60–79 years. PTSD at baseline predicted incident GAD, panic disorder, and specific phobia, whereas panic disorder at baseline predicted incident social phobia. In addition, personality disorder at baseline predicted incident GAD, panic disorder, and social phobia, but not specific phobia. Interestingly, after adjustment for other psychiatric disorders and sociodemographic factors, neither adverse life events nor measures of general health were related to incident anxiety disorder in this particular cohort (Chou et al., 2011; Mackenzie et al., 2011). It is not appropriate to compare the incidence rates from NESARC with the prevalence rates from NSMHWB as the age ranges, cohort characteristics, and diagnostic instruments all differed.

A significant minority of older people with an anxiety disorder also meet diagnostic criteria for a comorbid psychiatric disorder. For example, of older people with a DSM-IV 12-month anxiety disorder in the NSMHWB study, 60% met diagnostic criteria for a single anxiety disorder, 14% met criteria for at least one additional anxiety disorder, and 26% met criteria for at least one additional mood or substance use disorder. Similarly, of older people with a DSM-IV 12-month anxiety disorder, 78% had a comorbid physical disorder (Australian Bureau of Statistics, 2007). In contrast, of older NSMHWB participants with a 12-month history of affective disorder, 45.5% also had a 12-month history of anxiety disorder. These observations are important because there is a long-standing myth that pure anxiety disorder is uncommon in older people. Bereavement reactions are also commonly complicated by anxiety disorders, particularly GAD and PTSD (Zisook et al., 1990).

Although the prevalence of anxiety disorders in community-residing older people is lower than in young or middle-aged persons, older people with other health problems have been shown to experience a high prevalence of anxiety disorder. Smalbrugge and colleagues (2005) found that 29.7% of 333 Dutch nursing home residents had anxiety symptoms, 4.2% had subthreshold anxiety disorders, and 5.7% had an anxiety disorder. Residents with stroke or depression were at greater risk of an anxiety disorder. Chemerinski and colleagues (1998) assessed 398 patients with Alzheimer's disease and found that 5% met diagnostic criteria for GAD over the previous four weeks. In the Cache County study, Lyketsos and colleagues (2001) found that anxiety symptoms were present in 10–12% of patients with Alzheimer's disease of varying severities. Anxiety also occurs commonly in the context of mild cognitive impairment (Monastero et al., 2009). Moreover, it seems that individuals with normal cognition, but who are at increased risk of developing the clinical manifestations of Alzheimer's disease in the future, also have increased anxiety. Lavretsky and colleagues (2009) found that anxiety symptoms in middle-aged and older adults without dementia were associated with cerebral amyloid load, as demonstrated by 2-(1-{6-[(2-[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl}-ethylidene)malononitrile positron emission tomography (FDDNP-PET) binding.

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Burden of disease

The 2010 global burden of disease study aimed to identify all cases of DSM or ICD anxiety disorders worldwide and estimate associated levels of disability (Baxter et al., 2014). Anxiety disorders were ranked sixth in terms of years of life lived with disability (YLDs) in both high-income and low- and middle-income countries. There was marked regional variation in age-standardized disability-adjusted life years (DALYs) associated with anxiety, with the highest DALYs being found in North Africa, the Middle East, North America, Central Europe and Australasia and the lowest DALYs being found in East Asia, Eastern Europe, Sub-Saharan Africa, and Southeast Asia. DALYs associated with anxiety peaked in the 20- to 24-year-old age group and declined steadily with advancing age in both males and females.

In a total population study conducted in Denmark, mortality from natural and unnatural causes was increased in people with an anxiety disorder (Meier et al., 2016). For deaths from natural causes, the mortality rate ratio was 1.39 (95% CI: 1.28–1.51), and for deaths from unnatural causes, the mortality rate ratio was 2.46 (95% CI: 2.20–2.73).

Biological factors

Although the prefrontal cortex is involved in social cognition, it is the more phylogenetically ancient *limbic system* that is most involved in fear and anxiety responses. The limbic system includes the insular cortex, the cingulate gyrus, the hippocampus, and the amygdala. The amygdala is particularly important for the generation of panic (Davis, 1992) and there is evidence that fear responses in the amygdala are ‘hard-wired’ and difficult to extinguish (Sah and Westbrook, 2008). The presence of fear-related circuits involving the amygdala, insula, and anterior cingulate has been demonstrated in humans on neuroimaging studies with both functional magnetic resonance imaging (fMRI) and PET (Sehlmeyer et al., 2009).

The hippocampus modulates the activity of the hypothalamic–pituitary–adrenal axis, dampening down stress responses (Davis, 1992). There is evidence that both hippocampal volume and neurogenesis are implicated in the response to stress. Although more research in humans is needed, individuals with greater hippocampal volume and intact hippocampal neurogenesis appear to have greater resilience (Martin et al., 2009). In research on twins discordant for combat exposure in Vietnam, those with smaller hippocampi were vulnerable to PTSD following combat exposure, whereas twins with normal hippocampi or without combat exposure did not have an elevated rate of PTSD (Gilbertson et al., 2002). Thus, both the biological vulnerability demonstrated by small hippocampi and the environmental stimulus of combat exposure were necessary before PTSD developed.

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Studies in monozygotic and dizygotic twins indicate that about 30–40% of the variation in the risk of anxiety disorder is of genetic origin (Norrholm and Ressler, 2009). No genes of large effect have yet been identified (Schumacher et al., 2011), so polygenic influences are likely. There is some evidence that genetic factors might play a greater part in the aetiology of panic disorder than of GAD. Polymorphisms in the promoter region of the 5-HT transporter gene have been linked to risk of anxiety disorder (Xie et al., 2009). Individuals who are homozygous for the s allele of this promoter exhibit greater fMRI responses in the amygdala to fearful stimuli and report higher levels of neuroticism (Davis, 1992). In a study of survivors of the Rwandan genocide, Kolassa and colleagues (2010) found that the risk of PTSD depended upon both the traumatic load and the catechol-o-methyltransferase Val(158)Met polymorphism. Individuals with Val polymorphisms developed PTSD following trauma in a dose-response manner, whereas trauma-exposed individuals homozygous for the Met/Met polymorphism were at high risk of PTSD regardless of the level of their traumatic exposure. A meta-analysis which examined 14 studies with 15,883 subjects confirmed this association (Zhao et al., 2017). This same genetic polymorphism might also predict response to treatment (Lonsdorf et al., 2010), although more work is needed before these findings are translated into clinical practice.

Experiments in laboratory animals demonstrate the importance of the early environment in the development of anxiety. Rats separated from their mothers for several hours a day in the early postnatal period demonstrate increased hormonal reactivity to stress and increased anxiety-related behaviours (Kalinichev et al., 2002). In addition, rats raised by mothers with impaired licking and grooming behaviour are at increased risk of developing anxiety, with cross-fostering experiments indicating that this effect is mainly of environmental origin (Liu et al., 2000). Although it is clear that anxiety symptoms and anxiety disorders are due to a combination of genetic and environmental factors, a question that arises is whether genetic influences are less important in later life. Gillespie and colleagues (2004) found that this was not the case for late-life anxiety and depression, although there were differences between genetic influences in men and women. More specifically, there were additional midlife and late-life genetic influences in women. Thus, it seems that genetic effects are still operating strongly in later life.

Psychological factors

Normal anxiety is conventionally divided into trait anxiety and state anxiety. Both are dimensional rather than categorical constructs. Levels of trait anxiety are relatively stable over the lifespan, indicating the influence of genetic and early environmental influences. In contrast, levels of state anxiety fluctuate over time, reflecting responses to aversive stimuli throughout life. However, state anxiety is also influenced by genetic factors. In the dimensional ‘five-factor’ model of normal personality, high neuroticism is associated with anxiety symptoms and all anxiety disorders. In addition, high conscientiousness is associated with

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GAD and OCD, whereas low extraversion is associated with social phobia (Rosellini and Brown, 2011). In older adults, neuroticism and GAD are both moderately heritable (0.47 and 0.27, respectively), and approximately one-third of the genetic influence on GAD is shared with trait neuroticism (Mackintosh et al., 2006). Even in people with Alzheimer's disease, informant-rated premorbid neuroticism has been found to be associated with current anxiety on the Neuropsychiatric Inventory (Archer et al., 2007).

In both laboratory animals and humans, a new fear response develops when a harmless context or cue (conditioned stimulus (CS)) is paired with an aversive event (unconditioned stimulus (US)). Although the fear response to the CS can be extinguished by habituation—repeated exposure to the CS in the absence of the US—it is rapidly reinstated by either simultaneous re-exposure to the CS and US or sequential re-exposure to the US followed shortly by the CS, indicating that learned fear is strongly retained (Sah and Westbrook, 2008). This observation is likely to at least partially explain the chronicity of many anxiety disorders and why the response to short-term treatment is often poorly sustained. Avoidance behaviour leads to a temporary reduction in anxiety, which negatively reinforces (increases) avoidance behaviour. However, avoidance is not a successful long-term strategy as it makes anxiety worse by preventing habituation to the feared stimulus. Avoidance is thus key to maintenance of the fear response, and dealing with avoidance is critical to successful treatment of most anxiety disorders. Exposure and behavioural activation paradigms that reduce avoidance behaviours have been used as the basis for interventions for anxiety disorders (Cherbuin et al., 2008).

Hyperventilation is a common symptom of panic attacks, and for many years it was also considered to be a cause of panic (Griez and Schruers, 1998). However, inhaled carbon dioxide precipitates panic so it appears that it is hypercapnia, not hypocapnia, that leads to panic. This makes physiological sense, and has been referred to as the suffocation false alarm theory (Klein, 1993; Maddock, 2001). The relationships between panic, acid-base metabolism, and hyperventilation are complex and poorly understood, although it has been argued that chronic hyperventilation is a response to metabolic acidosis (Sikter et al., 2007).

There is evidence that anxiety disorders in later life are associated with childhood abuse or neglect. Analysis of data from the US National Comorbidity Study Replication (NCS-R) showed that childhood sexual abuse was associated with social phobia, panic disorder, GAD, and PTSD, whereas childhood physical abuse was associated with specific phobia and PTSD (Cougle et al., 2010). There is evidence also that childhood physical abuse is associated with an earlier age of onset of GAD (Gonçalves and Byrne, 2012a).

Anxiety symptoms

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Anxiety symptoms are diverse but are conventionally clustered under the three headings of physical, mental, and emotional. Physical symptoms are multifarious and can be experienced in any bodily system. They include palpitations, dyspnoea, chest tightness, dizziness, sweating, itch, blushing, nausea, teeth grinding, choking, butterflies in the stomach, diarrhoea, frequent urination, fatigue, weakness, muscle tension, tremor, and insomnia. Mental symptoms include worry, rumination, depersonalization, derealization, poor concentration, and memory impairment. Worry can be about many different topics. Emotional symptoms include fear, dread, anger, depression, emotional numbness, irritability, and tearfulness. Fear can be directed towards many objects or situations. Anxiety is also associated with a variety of behaviours, including avoidance of feared objects or situations, and repetitive checking or washing.

Panic

Panic attacks are conventionally defined as rapidly escalating anxiety episodes in which fear and apprehension rise to a crescendo within ten minutes and then subside over several hours. Panic attacks are associated with a wide variety of physical symptoms, including shortness of breath, tachycardia, palpitations, a choking sensation, chest tightness, sweating, tremor, paraesthesiae, nausea, and hot or cold flushes. People experiencing a panic attack commonly catastrophize about their symptoms and fear collapse, stroke, or death. Sometimes they think they will 'go crazy' or embarrass themselves in front of others. People having a panic attack often make frantic attempts to escape from the situation in which the panic attack occurred. They often go on to develop anticipatory anxiety about having further panic attacks.

Worry

Worry is a core manifestation of generalized anxiety and can be conceptualized as an attempt to solve feared events with uncertain outcomes (Borkovec et al., 1983). Overall, older people report fewer worries than young or middle-aged people (Lindesay et al., 2006; Coelho et al., 2010). Worry in later life is often directed towards different content areas than in younger adults. While older people are more likely than younger adults to worry about the health and welfare of loved ones, they are less likely to worry about work, health, and interpersonal relationships (Gonçalves and Byrne, 2013). Thus, there appear to be developmental aspects to worry content. At first glance, it might seem counterintuitive that older people should report fewer worries than younger people, given the common challenges of ageing and likely reduced opportunities for older people to habituate through exposure. The consistently verified reduction in worry frequency with age has been attributed to several complementary factors, including increased emotional regulation, changes in daily demands, the influence of cognitive habituation mechanisms, and cohort effects (Gonçalves and Byrne, 2013). Other factors, including data censoring due to premature

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death or institutionalization of worriers, and the use of assessment measures that are inappropriate for older people, might also explain some of the measured differences in worry prevalence (Gonçalves and Byrne, 2013).

Fear of crime among older people, especially older women, is a particular category of worry that is commonly promoted by mass media (Reiner, 2007). In most countries, it is associated with the paradox that older people are the least likely group to be either victims or perpetrators of crime. Of course, older people have lived longer than younger people and have thus had the opportunity to observe both more actual crime and more reports of crime. In a small US study, predictors of fear of crime among older people were found to be female gender, non-Caucasian ethnicity, depressive symptoms, and social isolation (Acierno et al., 2004). Housebound older women might experience greater levels of fear of violence than other groups (Barnett et al., 2007). In a UK study based on the Whitehall II cohort (middle-aged adults), fear of crime was associated with poorer physical and mental health and lower quality of life (Stafford et al., 2007). The specific association of fear of crime with anxiety disorders in later life needs further study.

Avoidance

Avoidance behaviour in older people can take many different forms and clinicians sometimes underestimate its severity and extent. Older people might avoid participating in everyday social activities by referring to commonplace physical complaints. They might give up driving a motor vehicle prematurely or stop doing the shopping. The risk for clinicians is that they might misinterpret this social withdrawal as the inevitable consequence of retirement or ageing, when it actually reflects avoidance behaviour associated with pathological anxiety. Identification of avoidance behaviour is important because avoidance makes anxiety worse, leading to its exacerbation and persistence. The persistence of avoidance behaviour in older people is often supported by well-meaning family members or carers, and sometimes by domiciliary services. Severe avoidance behaviour of the sort seen in agoraphobia almost always means that the patients have one or more supporters who help them maintain their behaviour. Even severe avoidance behaviour can be concealed for many years before coming to clinical attention, often precipitated by a change in care arrangements. Sometimes the term 'dependency' is used to describe the situation in which an older person is overly reliant upon others, although in many instances this should really be reframed as avoidance behaviour related to anxiety disorder.

Somatic symptoms

Older people have many more somatic symptoms than younger people due to the exponential rise in the prevalence of general medical problems with normal ageing. Older people are also thought to be more likely than younger people to minimize psychological symptoms and to convert

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psychological distress into physical symptoms, although it is unclear the extent to which this is a cohort effect or a direct effect of psychophysiological changes associated with ageing. It is often difficult for the clinician to disentangle the symptoms of general medical conditions from somatic symptoms of anxiety. Indeed, both types of somatic symptoms are often present simultaneously in the same person.

Obsessions and compulsions

Obsessional ruminations and compulsive rituals are core features of OCD but are also found in other mental disorders, especially major depressive disorder. Obsessional ruminations commonly involve aggressive, sexual, repugnant, immoral, or religious themes, on the one hand; or doubt, contamination, checking, superstition, symmetry, or order, on the other (Garcia-Soriano et al., 2011). They seem to exist on a continuum with intrusive thoughts experienced by individuals without OCD. The level of insight that accompanies obsessional phenomena varies, with some people with OCD believing that their intrusive thoughts will come true. In some cases of severe OCD, obsessional thoughts may be difficult to distinguish from delusions. Compulsive behaviours also appear to exist on a continuum with normal rituals and they can sometimes be difficult to distinguish from one another (Muris et al., 1997). Rituals generally involve similar themes to obsessional ruminations, and often involve washing and checking behaviours. True compulsions are generally more frequent, more intense, and associated with more affect than normal rituals. Starcevic and colleagues (2011) investigated the functions of compulsions in adults with OCD and, not unexpectedly, found that compulsions are usually performed automatically to decrease stress or anxiety.

Flashbacks

During a flashback the older person re-experiences a traumatic event during the waking state, in contrast to dreams or nightmares in which this occurs whilst asleep. Flashbacks are a core component of acute stress disorder and PTSD.

Depersonalization and derealization

In depersonalization, patients feel as though they are watching themselves as if in a dreamlike state. There is a sense of unreality about the self. In contrast, in derealization, patients feel a sense of unreality about the outside world. Depersonalization and derealization are common phenomena in people with anxiety disorders, and are part of the reason that panic attacks can be associated with a sense of impending doom or the thought that one is losing one's mind.

Anxiety disorders

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Panic disorder

To meet DSM-5 diagnostic criteria for panic disorder, panic attacks must be accompanied by at least four symptoms from a list, must peak within minutes, and must be unexpected. The practical problems with this definition are that panicky feelings are not always accompanied by the requisite four symptoms, do not always rise to a crescendo within minutes, and are often cued by contextual factors. As a consequence, panicky episodes are more prevalent than narrowly defined panic attacks, and subthreshold panic disorder is more prevalent than panic disorder. So, panic in older people is a larger clinical problem than the epidemiological data would suggest. While panic attacks are the defining feature of panic disorder, they occur in many other mental disorders, including major depressive disorder, GAD, alcohol withdrawal, and delirium. Older people with panic disorder are seen in the emergency department, where panic attacks mimic a variety of medical emergencies, including asthma and acute coronary syndrome. Panic attacks and panic disorder commonly precede the development of agoraphobia.

Agoraphobia

Agoraphobia involves fear and avoidance of situations from which escape might be difficult or in which help might not be available if a panic attack should occur (American Psychiatric Association, 2013). People with agoraphobia often avoid entering supermarkets, restaurants, or crowded shopping malls. They often have less trouble entering feared situations when accompanied by a trusted family member or friend. As time goes by, people with agoraphobia often gradually increase the range of situations they avoid, until they are quite limited in the situations they feel they can enter safely. People with agoraphobia tend to present for clinical care many years after the first onset of their panic attacks or avoidance behaviour. Agoraphobia is often a hidden problem in the sense that both patients and their family supporters tend to conceal it due to embarrassment.

Social anxiety disorder

People with social anxiety disorder (social phobia) experience fear, embarrassment, or humiliation in social situations, and experience anticipatory anxiety about forthcoming events. They avoid situations in which they feel other people may judge them. When avoidance is not feasible, they feel anxious and self-conscious around other people. Social phobia can be restricted to a certain social situation, such as public speaking, or it can be generalized. Social phobia can be precipitated by another psychiatric disorder, such as major depressive disorder or panic disorder. It is also commonly associated with substance use disorders, particularly alcohol abuse and dependence. Although social phobia is not an uncommon diagnosis in epidemiological surveys, older people with this condition rarely present for treatment. This might be because older people are not particularly disabled by social phobia due to reduced

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social and occupational demands in later life. There has been some controversy about the nosological status of social phobia, including concerns about medicalization of normal shyness.

Generalized anxiety disorder (GAD)

As conceptualized in DSM-5, the diagnosis of GAD requires the patient to have multiple worries that are experienced as excessive and that have persisted for six months or more. Older people with GAD report similar worry content to older worriers without GAD, but greater worry frequency (Diefenbach et al., 2001). This observation highlights the issue of whether GAD should be conceptualized as a dimensional disorder, rather than a categorical disorder. In comparison with non-pathological worriers, those with GAD differ also in the extent to which they can control their anxiety and in the level of distress associated with their anxiety (Ruscio, 2002). Worry is the predominant symptom in GAD, to the extent that Andrews et al. (2010) have argued that the disorder should be renamed *generalized worry disorder*, *major worry disorder*, or *pathological worry disorder*, in DSM-5. GAD appears to precede Major Depressive Disorder (MDD) more often than MDD precedes GAD. Gonçalves and colleagues (2011) found that GAD in older people was associated with functional limitations, psychiatric comorbidity, and increased medication intake.

Specific phobia

Specific phobia involves avoidance of feared objects (e.g. spiders, moths) or situations (e.g. flying, lifts). Although specific phobia is highly prevalent, it is not often the focus of therapeutic attention in old age psychiatry practice, mainly because it is generally associated with little distress or disability, apart from when the patient is actually confronted by the phobic stimulus. Older people are often able to avoid their phobic stimuli. Some specific phobias resolve without formal treatment, but some cause significant distress and disability.

Fear of falling is a relatively distinct psychosyndrome in later life with features of both specific phobia and agoraphobia (Coelho et al., 2010). It is associated with considerable disability for many older people. At least 30% of persons aged 65 years and over fall each year and one-fifth of these falls require medical attention (Stel et al., 2004). Falls are even more prevalent in older people with dementia (Allan et al., 2009) and in those taking psychotropic medication (Hill and Wee, 2012). Approximately one-quarter of those who fall develop fear of falling (McClure et al., 2005).

Post-traumatic stress disorder

PTSD is reported to develop in about 15–20% of older people exposed to life-threatening trauma but the measured prevalence might increase following removal in DSM-5 of the requirement to experience ‘intense fear, helplessness or horror’ at the time of the traumatic exposure

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(Friedman et al., 2011). Classically, PTSD follows combat exposure, armed holdup, rape, and violent assault. It is also seen in emergency workers required to deal with multiple trauma cases, and following disasters. In older people, PTSD has often developed earlier in life during military service, but can also develop *de novo* following adverse life events in later life. Sometimes PTSD does not develop immediately following exposure to the traumatic event, but following an extended delay. Characteristic symptoms of PTSD include intrusive re-experiencing of the traumatic event through flashbacks and nightmares. These intrusive phenomena are usually accompanied by hyperarousal, emotional numbness, and avoidance behaviour. Symptoms of hyperarousal include impaired concentration, lowered startle threshold, hypervigilance, and insomnia. Emotional numbness leads individuals to feel that they can no longer experience emotions normally and that their interpersonal relationships are impaired. Avoidance behaviour commonly involves avoiding the scene of the traumatic exposure or avoiding reminders of the trauma. Many other symptoms occur in PTSD, including dissociation and substance abuse. In older people, PTSD has often been present for many years following combat exposure or wartime rape and other atrocities. Older refugees are particularly at risk of PTSD. Older victims of natural disasters such as floods, fires, and earthquakes are also at risk of PTSD.

Obsessive-compulsive disorder

OCD is characterized by obsessional ruminations and compulsive rituals. Obsessions are thoughts, images, and impulses that lead to psychological distress. Patients experience obsessions as being the product of their own mind and generally have insight into them. Compulsions can be observable behaviours (rituals) or unobservable behaviours (mental compulsions). Compulsions are considered to represent an attempt by the patient to undo obsessional thoughts, prevent harm, or reduce anxiety. Although obsessions and compulsions are the defining characteristics of OCD, they do occur in other mental and neurological disorders.

Of particular relevance to OCD in older people, hoarding is often performed because of a perceived need for collected objects rather than for reasons common to other compulsions. Hoarding behaviours appear to occur commonly in the general population (Timpano et al., 2011) and are linked to compulsive buying behaviours (Mueller et al., 2009). There is also evidence that hoarding is associated with multiple neurological and psychiatric disorders, including depression and anxiety (Mataix-Cols et al., 2011; Reid et al., 2011). Hoarding also overlaps with severe domestic squalor (Snowdon and Halliday, 2011). Moral or religious scrupulosity is often viewed as a symptom of OCD. Although more commonly encountered in older members of the clergy, it can be seen among laity as well.

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Mixed anxiety and depression

Some older people experience a mixture of anxiety and depressive, although the prevalence of these mixed states is in dispute. As previously noted, there is some comorbidity between GAD and major depressive disorder. In addition, there is a group of older people who experience symptoms of both anxiety and depression without meeting diagnostic criteria for a mood or anxiety disorder. The diagnostic entity of mixed anxiety and depressive disorder exists in ICD-10 and ICD-11, but not DSM-5. Because of the dimensionality of both anxiety and depressive symptoms, and because mixed subthreshold states appear to be common among older people, this is a useful diagnostic category.

Anxiety and agitation in dementia

One question that arises is can *anxiety* be distinguished from the *agitation* associated with dementia? It is difficult to give a straightforward answer to this question because both anxiety and agitation are words that describe complex arrays of human behaviours. There is clearly some overlap between the constructs (Twelftree and Oazi, 2006), but also many differences between the two. The term agitation is commonly used to describe a broad range of behaviours in people with dementia. Agitation is also used to describe a category of behaviour in people with delirium and a different category of behaviour in people with depression. So, the legitimate question arises if anxiety can reliably be distinguished from agitation? In a large factor analytic study of untreated patients with dementia due to Alzheimer's disease, Spalletta and colleagues (2010) found that anxiety and agitation loaded on separate factors. Anxiety loaded on a factor with depression, whereas agitation loaded on a factor with irritability and aberrant motor behaviour. Although this finding alone is unlikely to settle the matter, it does suggest that these terms should not be conflated.

Anxiety and suicide

There is robust evidence linking suicide attempts with anxiety disorders. Using data from the US NESARC study, Nepon and colleagues (2010) found that among adults reporting a lifetime history of suicide attempts, 70% had an anxiety disorder. In multivariate models, PTSD and panic disorder were independently associated with suicide attempts. Individuals with PTSD or panic disorder who also had a personality disorder had an even greater risk of suicide attempts (Nepon et al., 2010). In a 15-year national clinical survey of suicide in the UK, Voshaar and colleagues (2015) found that of the 4,481 persons aged 60 years and over who died by suicide, 742 (16.6%) had either a primary or a comorbid anxiety disorder.

Assessment

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Every psychiatric assessment interview should include screening questions for anxiety symptoms, given the high prevalence of anxiety symptoms and anxiety disorders. At a minimum, worry, panic, obsessions, and compulsions should all be covered. It is important to be aware of limited-symptom panic attacks. These subthreshold panic attacks are characterized by fewer than the four panic symptoms required by DSM-5 definition of a panic attack. The clinician should also make specific inquiry about the nature and extent of avoidance behaviour in older people presenting with anxiety symptoms. Avoidance behaviour can manifest as 'taking to the bed' with non-specific somatic symptoms, or be more subtle or camouflaged in some way, perhaps with the older person declining routine social invitations, only leaving the home in the company of others, not watching the television news, or avoiding talking about or even thinking about certain topics. As anxiety increases the risk of suicide attempts, the clinician should ensure that suicidality is covered during the assessment of older people with anxiety. Anxiety often flares up in response to adversity, so assessment of exposure to adverse life events is essential. A life-history approach is often useful to chart the correspondence between life events and anxiety symptoms. If a behavioural intervention is intended, then a behavioural analysis is a necessary preparatory step.

Informant interviews

Informant interviews are an essential component of the assessment of older people with suspected cognitive impairment or dementia. They are also useful in older people with anxiety disorders. Some older people minimize the extent of their avoidance behaviour or the relationship of this to their anxiety symptoms. An appropriate informant, usually a close family member, can often shed useful light on this avoidance behaviour. An informant can also often provide collateral information about the use of substances, including alcohol and benzodiazepines. In most countries, older people are free to consult as many different doctors as they wish. In so doing, they are at liberty to obtain multiple prescriptions for sedative and hypnotic drugs. When older people with anxiety disorders are seen in specialist settings, they have generally been referred by only one of the doctors with whom the patient has had contact. In such circumstances, an informant can provide an important insight into the drug-seeking or drug-using behaviour of the patient. Of course, consent must be obtained from the patient before consulting an informant.

Rating scales

It is often useful to measure the severity of anxiety during assessment or treatment. Many scales are available to measure anxiety in adults, but very few have been specifically designed for use in older people. Self-report scales for use by older people, particularly the frail older person, require certain modifications. Ideally, such measures should avoid multiple somatic items, reversed items, and complex response scales (Dennis et al., 2007). The Short Anxiety Screening Test (SAST) is a 10-

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item self-report measure with a four-item response scale (Sinoff et al., 1999). The SAST was designed specifically for use in older people, although it does contain multiple somatic items. The Geriatric Anxiety Inventory (GAI) is a 20-item self-rating scale designed to assess generalized anxiety in older people (Pachana et al., 2007a). It employs straightforward language and dichotomous (agree/disagree) ratings, and minimizes the use of somatic items. There is also a five-item version for screening (Byrne and Pachana, 2011). The GAI is now available in 20 languages. The Geriatric Anxiety Scale (GAS) is a 30-item self-rating scale with a four-item response scale (Segal et al., 2010). There is also a ten-item version of the GAS. The psychometric properties of the GAI and the GAS were compared in a sample of 110 older people with a mean age of 75 years (Gould et al., 2014). Both the GAI and GAS had good psychometric properties, with the GAI having better discriminant validity.

Substance abuse

Older people with clinically significant anxiety often abuse alcohol or benzodiazepines. They frequently minimize their intake of these substances or minimize the likely link between their intake and their anxiety symptoms. Substance abuse and dependence can be the direct cause of anxiety symptoms or can be the consequence of self-medication of a pre-existing anxiety disorder. In older people with mild cognitive impairment or dementia, particularly those living alone, alcohol abuse can be unsuspected, even by members of their immediate family. In office practice, it helps to have a knowledgeable informant who can provide collateral information about substance use. A domiciliary visit can often help clarify an older person's likely alcohol intake. Clinicians should maintain a high index of suspicion for substance abuse and dependence in older people with anxiety disorders.

Medications associated with anxiety

Many medications used to treat mental disorders and general medical conditions are associated with anxiety symptoms, and sometimes the most effective intervention is the cessation of unnecessary medication. Sympathomimetics, corticosteroids, oestrogen, antihistamines, interferon, TNF-alpha, and thyroid hormones have all been associated with anxiety symptoms. In addition, psychotropic drugs, including anxiolytics, antidepressants, mood stabilizers, and antipsychotics can cause anxiety symptoms.

Physical work-up

Older people who present with anxiety symptoms for the first time in later life should be investigated for underlying general medical problems. Even those older people who have a distant past history of anxiety symptoms but who have been symptom-free for many years should undergo screening tests for potential underlying general medical problems. At a minimum, a systems review should be undertaken and vital signs should be recorded. In first-onset cases of anxiety disorder in later life, more

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detailed neurological and cardiovascular examination is prudent. Selected laboratory tests, including full blood examination, serum electrolytes, serum glucose, thyroid stimulating hormone (TSH), and urinalysis should be ordered. If psychotropic medication is to be prescribed, then pre-treatment liver function tests and an electrocardiogram (ECG) should be added to the list. If there is any suggestion of substance abuse then a urine drug screen should be ordered. Electroencephalography (EEG) can help exclude epilepsy and delirium, if these are suspected clinically. Neuroimaging has a low yield in late-life anxiety disorders, but if underlying cerebrovascular disease is suspected then a structural brain scan (MRI or CT) might be warranted to assess the extent of this. Serological tests for syphilis, hepatitis, HIV, and other infections should be reserved for particular cases in which the history suggests greater than normal risk. Older patients with unusual presenting symptoms should undergo more detailed physical investigation.

Management

There is actually quite a lot for the clinician to do when managing anxiety in older people. Paying close attention to some straightforward general principles is likely to greatly assist the patient, so these are described here first. Anxiety of moderate severity or greater is likely to require formal psychological treatment, pharmacological treatment, or both. Several classes of drugs have been used in the treatment of anxiety symptoms and anxiety disorders in older people and several types of behavioural and psychological treatments have been used.

General measures

Substance use

Both excessive consumption of nicotine, caffeine, and alcohol and withdrawal from these substances are commonly associated with anxiety symptoms. People with anxiety disorders also self-medicate with these substances. Some older people require specific advice about minimizing their exposure to these legal substances. Medications used to treat general medical conditions may also be associated with anxiety and insomnia. These include sympathomimetics, corticosteroids, thyroid hormones, antimicrobials, oestrogen, and antihistamines. Diuretics commonly disrupt sleep and are generally best taken earlier in the day. Stimulants including methylphenidate and dexamphetamine are used occasionally to treat adult attention deficit hyperactivity disorder (ADHD) and apathy in older people. These medications are commonly associated with weight loss, insomnia, and anxiety. Some antidepressant medications have stimulant effects in vulnerable older people, and selective serotonin reuptake inhibitors (SSRIs) commonly cause an initial increase in anxiety and insomnia.

Although older people are less likely than young or middle-aged people to use illicit substances, there are cohort effects at work that might lead to

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increased rates of substance abuse in older people in the future (Wu and Blazer, 2011). Cannabis, amphetamine, cocaine, and opiates can all cause anxiety symptoms. Thus, a careful review of current substance use, both licit and illicit, is recommended.

General medical conditions

Many general medical conditions are associated with anxiety, either directly or indirectly. Although a direct mechanism has not been fully elucidated, it is likely to involve cytokine production at sites of inflammation. An indirect mechanism involves a psychological reaction to pain, discomfort, and disability, as well as increased dependency upon others and a sense of an altered future, associated with many diseases. Hyperthyroidism, paroxysmal supraventricular tachycardia, atrial fibrillation, asthma, chronic obstructive lung disease, epilepsy, and systemic lupus erythematosus have all been associated with anxiety disorder. Parkinson's disease is associated with a particularly high rate of anxiety disorder (Broen et al., 2016). Thus, optimal management of patients' general medical conditions is an integral component of management of their anxiety disorder.

Physical activity

In older people, physical activity has general benefits for health, particularly in maintaining or improving bone density, muscle strength, and cardiovascular fitness. In addition, physical activities such as walking, cycling, and swimming have anxiolytic effects. Exposure to interoceptive stimuli, such as increased rate and depth of breathing, increased heart rate, and perspiration, acts as a form of non-specific exposure in people with anxiety disorders. This exposure to interoceptive stimuli is associated with reduced anxiety sensitivity (Barbour et al., 2007). If the physical activity is undertaken outdoors, or in a public setting such as a gym, it also acts as exposure to exteroceptive stimuli.

Sleep hygiene

Sleep architecture changes gradually with increasing age and sleep continuity declines in many older people (Harbison, 2002). Some people interpret these normal changes as indicative of a sleep disorder, when they are not. Nevertheless, insomnia does reduce the quality of life of many older people, particularly those who suppress their REM sleep with hypnotic medication, or those who worry excessively about their sleep continuity or duration. Improvements in sleep duration and quality can lead to reduced anxiety. Routine sleep hygiene recommendations include ensuring that the sleeping environment is satisfactory. In practice, this means having a comfortable bed and pillow, maintaining the bedroom at an appropriate temperature, and ensuring the sleeping environment is both quiet and dark. It is also important to reserve the bedroom for sleep and sexual activity, and not remain in bed if unable to sleep. In this way, the bedroom is associated with sleep, rather than wakefulness. It is also

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recommended that people with a sleep initiation problem do not undertake vigorous physical exercise in the hours immediately before bedtime, although physical exercise during the day generally assists initiation and maintenance of sleep (Loprinzi and Cardinal, 2011).

Because of their potential to stimulate some people with insomnia, it is recommended that television and other electronic displays should not be watched in the bedroom. From a behavioural perspective, it is useful to have a bedtime routine that conditions one to expect sleep.

Psychological interventions

For pragmatic reasons, psychotropic medications are commonly used as first-line treatments for anxiety disorders in older adults, particularly in primary care settings. However, expert opinion generally advises the use of a psychosocial intervention for anxiety disorders of mild to moderate severity and combination treatment with a psychosocial intervention and a psychotropic medication for more severe anxiety disorders. In old age psychiatry services, most anxiety disorders will be at least moderate in severity and will often occur in comorbid relation to other disorders, including mood disorders, psychotic disorders, and substance use disorders. Thus, combination treatment with a psychosocial and psychopharmacological intervention will generally be indicated in these specialist mental health care settings.

Therapeutic alliance

A supportive relationship with a mental health clinician is likely to be of considerable value to the anxious older person, and time spent developing a durable therapeutic alliance is well worth the investment. Psychological and behavioural interventions that provide older people with an improved set of coping skills are likely to be of enduring benefit to them. Older people with anxiety disorders are often helped by a longer-term relationship with a mental health worker. Patients who are allocated to medical personnel who move rapidly through different treatment teams as part of their training should also be allocated a case manager or staff psychologist who has a continuing appointment. In this way, continuity of care can be provided. An effective therapeutic alliance is likely to be particularly important if the clinician will be recommending to the patient either formal exposure therapy (e.g. systematic desensitization) or a reduction in avoidance behaviour. The perceived counterintuitive nature of these interventions requires patients to trust their clinicians to a greater extent than usual.

Psychoeducation

Many older people with anxiety symptoms and anxiety disorders suspect that they have serious physical problems. As a consequence, psychoeducation is an essential component of any anxiety management plan. In some cases, psychoeducation alone leads to a clinically significant improvement in anxiety symptoms as the older person reframes their problem. In people with cognitive impairment or

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intellectual disability it is essential that psychoeducation is provided to their family and carers.

Relaxation training

Relaxation training is an essential component of the treatment of anxiety symptoms and anxiety disorders in older people. Many different types of relaxation training have been described, although three techniques are in common use: progressive muscular relaxation, reciprocal inhibition via visual imagery, and controlled breathing. Progressive muscular relaxation is most suitable for those older people without significant sarcopenia or joint deformity, whereas the other two techniques can be used by most older people without cognitive impairment.

Cognitive behaviour therapy

There is a growing body of evidence in support of the use of cognitive behaviour therapy (CBT) to treat GAD in older people. A meta-analysis of CBT versus control conditions for GAD in older people identified 11 small clinical trials with usable data (Gonçalves and Byrne, 2012b). CBT was superior to control conditions with a pooled odds ratio of 0.33 (95% CI: 0.17–0.66). The superiority of CBT was demonstrated in those studies that used usual care or a waiting list as the comparison condition, but not in those that compared CBT to an active comparator. This observation raises questions about the specificity of CBT and suggests that other interventions could have similar efficacy. Similar findings have been reported from a randomized controlled trial of group CBT targeting tolerance of uncertainty in older people with GAD undertaken in Beijing, PRC (Hui and Zhihui, 2017). Suitable modifications for the use of CBT or its components in older people have been detailed by Laidlaw and colleagues (2003) and by Pachana and colleagues (2007b). These include an increased number of sessions to allow more time for participants to develop an understanding of the therapy and its associated homework tasks, explicit learning aids, and manuals with larger print size. CBT techniques are also used in the management of several other anxiety disorders in older people, although without the same level of empirical evidence. Various modifications to CBT have been elaborated. Roberts and Sedley (2016) detailed the rationale for acceptance and commitment therapy with older people, and Helmes and Ward (2017) demonstrated the efficacy of mindfulness-based cognitive therapy for anxiety symptoms in older nursing home patients.

Behaviour therapy

In some older people with anxiety disorders, it is not practicable to implement the cognitive components of CBT. This can occur when the older person has significant cognitive impairment or intellectual disability. It can also occur when older people do not view their problem in psychological terms and remain impervious to psychoeducation. In such situations it makes sense to apply behavioural interventions alone.

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The principles of behavioural activation can be employed (Ekers et al., 2011; Snarski et al., 2011). These emphasize graded activity scheduling and a reduction in avoidance behaviours. In one study involving adults with major depression, behavioural activation outperformed CBT and was comparable to antidepressant medication (Dimidjian et al., 2006). There is preliminary evidence that such an approach might be applicable to older adults with anxiety disorders as well (Pachana et al., 2007b).

Exposure therapy is the treatment of choice for agoraphobia, social phobia, and specific phobia. As flooding is rarely appropriate or practicable, systematic desensitization is the usual exposure method employed. This involves the preparation of a hierarchical list of phobic cues in close consultation with the patient. The phobic cues are listed from least aversive to most aversive. Exposure tasks are then designed to enable the patient to systematically work through the list from least aversive to most aversive. An individualized approach is necessary, as the time needed to master each step will vary from patient to patient. Many patients find themselves unable to engage in exposure therapy without the assistance of a confederate. This should usually be a clinician rather than a family member, as family members often overtly or covertly sabotage exposure activities. However, the ultimate aim of systematic desensitization is for patients to be able to repeatedly expose themselves to the phobic object or situation without the assistance of another person. In OCD, compulsive rituals are generally treated with exposure and response prevention. This is an effective treatment when rigorously applied. Obsessional ruminations can be treated with either antidepressant medication or CBT, or both. Because exposure therapy does lead to a temporary increase in psychological distress, it must be undertaken with the informed consent of the patient. Deception is not part of exposure therapy for anxiety disorders.

Interpersonal psychotherapy

Interpersonal psychotherapy (IPT) uses four principal models to engage the patient. These models address i) issues that arise in relation to grief following loss of a loved one, ii) conflict in relationships, iii) adapting to change in life circumstances, and iv) social isolation. It is not difficult to see that generalized anxiety symptoms and phobic avoidance behaviour could easily arise in relation to each of these challenges that occur commonly in later life. Despite this, there are limited data in support of the use of IPT in the management of anxiety disorders in older adults, although it is used for the management of depression in late life (Reynolds et al., 1999).

Problem-solving therapy

A reduced capacity to solve everyday problems has been linked, directly and indirectly, to anxiety. The indirect link is with impaired problem-solving and worry, which in turn lead to anxiety (D’Zurilla and Nezu, 2007, pp. 80-81). The clinical approach to problem-solving therapy

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involves iterative cycles of problem definition and formulation, generation of alternative solutions through brainstorming and other techniques, and identification of the most effective solution (D’Zurilla and Nezu, 2007, pp. 95–148). Although much of the research on problem-solving therapy has been conducted in young and middle-aged persons, or in older people with depression rather than anxiety, there has been some recent work in older adults with anxiety. In a pragmatic randomized controlled trial conducted in the Netherlands, six weeks of bibliotherapy involving problem-solving techniques and systematic desensitization was superior to treatment as usual in older primary care patients with an anxiety disorder but no comorbid depression (Seekles et al., 2010). In contrast, a Hong Kong clinical trial that compared brief problem-solving therapy with group viewing of health videos in primary care patients with elevated Hospital Anxiety and Depression Scale scores did not find a significant difference between treatment arms (Lam et al., 2010). There is evidence of the superiority of problem-solving therapy to supportive therapy in older people with depression (Alexopoulos et al., 2011), but further research is needed in older people with anxiety disorders in order to establish the place of PST in late-life anxiety disorders.

Other types of therapy

If anxiety symptoms arise in the context of interpersonal conflict, within a marital relationship or its equivalent, or within a family, then consideration should be given to couples therapy or family therapy. Psychoanalytic psychotherapy has been used historically to treat chronic anxiety symptoms, but not commonly in older people. There is little conventional evidence for this approach in this age group.

Medication

Drug therapy is generally unhelpful in the management of specific phobias, which usually respond to behaviour therapy, particularly exposure-based treatments employing systematic desensitization. Drug therapy does have a role in the management of the other anxiety disorders, particularly in combination with some type of psychotherapeutic intervention. A meta-analysis of clinical trials of psychotropic medication for GAD in older people identified nine brief clinical trials with usable data, including eight trials with a placebo comparator (Gonçalves and Byrne, 2012b). Medication was superior to the control condition with a pooled odds ratio of 0.32 (95% CI: 0.18–0.54). Benzodiazepines, antidepressants, and quetiapine all demonstrated short-term efficacy.

Benzodiazepines

Benzodiazepines operate at the GABA_A receptors of the brain’s main inhibitory neurotransmitter GABA (γ-aminobutyric acid). There is cross-reactivity with alcohol at this receptor complex. Benzodiazepines remain in widespread use in older people with anxiety disorders, although the evidence in support of their use is rather limited. They appear to have

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short-term efficacy in the management of panic attacks, generalized anxiety, and insomnia. However, their long-term effectiveness is uncertain and their use is associated with a range of adverse effects in older people, including anterograde amnesia, confusion, and falls. Tolerance develops rapidly and abrupt cessation of benzodiazepines is often associated with withdrawal phenomena. Both patients and clinicians find it difficult to distinguish benzodiazepine withdrawal phenomena from the pre-existing anxiety, thus perpetuating the use of these agents. Benzodiazepines suppress REM sleep (Hemmeter et al., 2000) and rebound effects can be encountered following their withdrawal. Withdrawal phenomena appear most severe following long-term use of high doses of short-acting agents. A small proportion of older people prescribed benzodiazepines develop paradoxical effects such as excitement or agitation. When benzodiazepines are used in the management of anxiety symptoms, including insomnia, they should ideally be used for short periods (two to four weeks) while other treatments are introduced. Drugs such as oxazepam and temazepam, which do not undergo hepatic oxidation, are generally preferred in older people. Because of its slow rate of absorption, oxazepam is useful for the treatment of middle insomnia, whereas temazepam is more useful for initial insomnia. Modern benzodiazepine replacements such as zopiclone, zolpidem, and zaleplon have shorter half-lives than the benzodiazepines and are less likely to be associated with morning sedation. However, they otherwise seem to confer few advantages. Although the benzodiazepines have short-term efficacy in many of the anxiety disorders, they are considered ineffective in OCD and of limited value in PTSD.

Antidepressants

Antidepressants are preferred for the pharmacological treatment of the anxiety disorders, although their use in this context does have some challenges. The SSRI antidepressants are the usual first-line medications in older people with panic, social phobia, GAD, OCD, and PTSD. They appear to be of no value in specific phobia. SSRIs take effect much more slowly than benzodiazepines, with longer-term effects on the sensitivity of auto-receptors leading to increased availability of synaptic 5-HT. The SSRIs are commonly associated with an initial increase in tremor, insomnia, and anxiety, and anxious older patients should be warned about this, lest they become concerned that their underlying disorder is deteriorating. It is sometimes necessary to use a low-dose benzodiazepine for a week or two to get the patient through the initial adverse effects of an SSRI, particularly in somatically focused patients. A greater challenge for prescribers is that patients who have had experience with the rapid onset of action of the benzodiazepines are often dissatisfied with the relatively slow onset of action of antidepressants. There appears to be little to choose between the available SSRI antidepressants in terms of their anxiolytic effects. However, paroxetine has more anticholinergic effects than the other drugs in this class and for this reason is generally less favoured in older people. The long half-life of fluoxetine is associated

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with both risks and benefits, but fluoxetine is generally not the first choice in older people. Citalopram and escitalopram are associated with prolongation of the electrocardiographic QTc interval and it has been recommended that they be restricted to 20 mg and 10 mg daily, respectively, in older people (Medicines and Healthcare Products Regulatory Agency, 2011). Fluvoxamine is a sedating SSRI, which is often well tolerated in anxious individuals, although it does have a greater potential for drug–drug interactions than the other drugs in its class due to effects on the hepatic enzyme system.

The SSRIs have significant adverse effects in older people. These include initial worsening of anxiety and insomnia, hyponatraemia, sexual dysfunction, and falls. They are also associated with increased bruising and bleeding in patients on anticoagulants and antiplatelet drugs. Hyponatraemia occurs most commonly in women on thiazide diuretics, and often within six weeks of initiating antidepressant treatment. The symptoms of hyponatraemia can mimic those of worsening anxiety or depression, and can also include fatigue and confusion. The true prevalence of hyponatraemia is unknown but it is a frequent occurrence on inpatient wards. The clinician is advised to check the serum sodium in older patients on antidepressant medication whose clinical condition is deteriorating. All antidepressants can precipitate mania and hypomania in vulnerable individuals, but this is relatively uncommon and is not a reason to avoid these drugs in older people with clinically significant anxiety. The reported increased risk of suicide in patients commenced on SSRI antidepressants does not seem to be relevant to older people, in whom treatment with SSRIs is associated with a reduced suicide risk (Barbui et al., 2009).

Other classes of antidepressants, including the serotonin and noradrenaline receptor inhibitors (e.g. venlafaxine, desvenlafaxine, duloxetine), drugs with mixed receptor activity (e.g. mirtazapine), and the older tricyclic drugs are also used in the pharmacological management of anxiety in older people. Among the tricyclic antidepressants, nortriptyline appears to have the best safety profile in older patients. Historically, clomipramine has had a special place in the treatment of severe OCD, although its adverse effect profile makes it challenging to use in many older people. However, it is not entirely clear whether clomipramine is superior to intensive exposure and response prevention (Foa et al., 2005). The noradrenaline reuptake inhibitor reboxetine and the older, irreversible, monoamine oxidase inhibitor drugs are not usually used in the management of anxiety disorders in older people. The serotonin antagonist and reuptake inhibitor (SARI) trazodone does have anxiolytic effects, but it is not well studied in older people with anxiety disorders.

The 5HT_{1A} receptor partial agonist buspirone has been used in treatment of GAD in older people for many years. It has a slow onset of action and seems to be most useful in benzodiazepine naïve patients. It has a number of drug–drug interactions and should not be used by people who are currently taking or who have recently been taking monoamine

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oxidase inhibitors. Agomelatine is an antidepressant with melatonergic (MT₁, MT₂) receptor agonist and 5-HT_{2A} receptor antagonist properties that appears to reduce sleep latency without causing daytime drowsiness. There is some limited evidence for its efficacy in GAD in adults (Stein et al., 2008), but there have been no clinical trials for this indication in older people.

In older people, antidepressants are generally commenced at half the usual starting dose used in younger adults and the dose is titrated upwards more slowly. Sometimes the final antidepressant dose is lower than that used in younger people, although many older people require the same final doses as younger people to achieve efficacy. As a broad generalization, the antidepressant dose required to treat anxiety disorders is often the same or greater than that required to treat depression.

Antipsychotics

Atypical antipsychotic drugs, particularly quetiapine and risperidone, are sometimes used in the management of the symptoms of both GAD and PTSD in adults. However, evidence for the use of antipsychotics for these indications in older adults is meagre (Ahearn et al., 2011; Gonçalves and Byrne, 2012b). Cerebrovascular adverse events (strokes and transient ischaemic attacks) and excess mortality have been described in association with the use of antipsychotic medication in older nursing home residents with dementia complicated by behavioural and psychological symptoms (Sacchetti et al., 2010), although a case-control study conducted in patients with dementia in the primary care setting did not identify similar problems (Laredo et al., 2011). Nevertheless, it would seem prudent to minimize the use of antipsychotic medication in older people with nonpsychotic disorders in the absence of long-term efficacy and safety data.

Anticonvulsants

There is some evidence for the use of anticonvulsants in adults with anxiety disorders, including the use of gabapentin in social phobia, lamotrigine in PTSD, and pregabalin in social phobia and GAD (Mula et al., 2007). However, there is a scarcity of evidence relating specifically to the use of anticonvulsants in older people with anxiety disorders.

Other drugs

Lithium carbonate is rarely used for the treatment of anxiety disorders, apart from when it is used to augment other agents that are being used to treat comorbid disorders. Lithium is not recommended for the treatment of older people with anxiety disorders. Beta-adrenergic blockers, principally propranolol, have been used to reduce performance-related tremor in musicians. Clonidine has been used to assist in the management of preoperative anxiety.

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Conclusion

Anxiety disorders occur commonly in older people and are associated with considerable emotional distress and disability. Anxiety disorders in later life tend to be both underdiagnosed and undertreated. Anxiety disorders are often seen in comorbid relation to other mental disorders and to general medical conditions. Effective treatments exist for anxiety disorders, although greater effort is needed to make these treatments routinely accessible to older people, including those with physical frailty or cognitive impairment.

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Late-onset schizophrenia

Chapter: Late-onset schizophrenia

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Introduction

The literature on late-onset schizophrenia (LOS) is growing, although slowly. It points to important diagnostic, treatment, and prognostic differences from the more common early-onset schizophrenia (EOS). Yet, there remain some gaps in our understanding (Jeste and Nasrallah, 2003), suggesting a need for further research. As of 2000, it was estimated that only 1% of the literature on schizophrenia focused on the older population, with an even smaller proportion specific to the late-onset subgroup (Cohen et al., 2000). Unsurprisingly, schizophrenia with onset in late life remains a challenge to both clinicians and researchers, despite the one-year prevalence rates of 0.6% and 0.2% among individuals aged 45–64 years and 65 years and over, respectively, and lifetime prevalence of 1% and 0.3% reported by the Epidemiologic Catchment Area (ECA) study (Robins and Regier, 1991) and the rising numbers of older adults.

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Research on this topic has been hampered by lack of consensus regarding nomenclature and diagnostic criteria as well as heterogeneity in clinical samples, often resulting in a variety of clinical syndromes included under the same broad diagnostic category (Castle and Morgan, 2008). For example, 'late-life schizophrenia' is an umbrella term that can be applied to two different groups of individuals: those diagnosed with schizophrenia in early adulthood and those who developed the illness in middle or late life (Palmer et al., 1999).

A significant increase in the older population is expected, resulting in a doubling of the number of seniors with severe mental illnesses by 2050 (Cohen et al., 2000). More frequent cases of LOS are to be expected, but it needs to be emphasized that individuals with onset of symptoms prior to age 45 will still account for approximately 85% of patients with schizophrenia encountered in clinical settings (Cohen et al., 2000). In this chapter, we focus primarily on schizophrenia first manifesting in late life, and subsequently on chronic schizophrenia in older people and its distinction from LOS.

Nomenclature

Historical background

While the current terms late-onset schizophrenia (LOS) and very-late-onset schizophrenia-like psychosis (VLOSLP) have gained acceptance in recent years, previous terms such as late paraphrenia and the French term *psychose hallucinatoire chronique* remain in use occasionally in the world literature and are commonly used by clinicians, especially outside the US (Dubertret et al., 2004; Harris and Jeste, 1988; Howard et al., 1994; Riecher-Rössler et al., 2003).

In his use of the term 'dementia praecox', Kraepelin (1899) implies an early onset and rapidly deteriorating course. A decade later, Eugen Bleuler (1950) de-emphasized age of onset as a defining feature. Kraepelin later recognized that sometimes the illness presented later in life and he described cases with onset as late as the seventh decade, although these accounted for only 0.2% of the 1,054 patients he studied.

Manfred Bleuler, Eugen's son, may be considered the first to explicitly introduce in 1943 the concept of LOS. Setting the ground with criteria still applied today, he stated that these cases should begin after age 40, with symptoms not fundamentally different to those seen in schizophrenia with an earlier onset, and that there should be no amnesic syndrome or physical sign that indicated a degenerative brain disease as the most likely aetiology (Bleuler, 1943). Using this definition, he found that 15% of schizophrenic disorders began between 40 and 60 years of age, with only a small number of cases presenting later. Prior to Manfred Bleuler's work, others in Germany had attempted to distinguish cases of later onset, including Gaupp in 1905, followed by Stransky ('dementia tardiva'), Berger ('paranoia chronica'), Kleist ('involutional paranoia'), Albrecht

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(‘presenile paraphrenia’), Serko (‘involutional paraphrenia’), and Medow (‘stiffening involutional psychosis’). British psychiatrists employed the term ‘late paraphrenia’ to describe ‘a well-organized system of paranoid delusions with onset after age 45, with or without hallucinations existing in the setting of a well-preserved personality and affective response’ (Roth, 1955). Post (1966) doubted the frequency of schizophrenia with onset in late life and felt that a heterogeneous group of disorders were more likely, hence the expression ‘persistent persecutory states of late-life’.

The *Diagnostic and Statistical Manual (DSM)* has changed its stance on distinguishing late-onset from earlier-onset schizophrenia over the past four editions. Published in 1980, the DSM-III had eliminated the category ‘involutional paranoid states/paraphrenia’ and did not allow for the diagnosis of schizophrenia if symptoms emerged after the age of 45 (American Psychiatric Association, 1980). This criterion was modified in the revised edition with the introduction of the ‘late-onset’ specifier for onset after 44 years old (American Psychiatric Association, 1987). However, the term was eliminated from the DSM-IV (American Psychiatric Association, 1994) and the DSM-5, which notes, ‘Such late-onset cases can still meet the diagnostic criteria for schizophrenia, but it is not yet clear whether this is the same condition as schizophrenia diagnostic prior to mid-life (e.g., prior to age 55 years)’ (American Psychiatric Association, 2013, p. 103). The World Health Organization included no qualifier for late-onset in its *International Classification of Diseases, 8th edition* (ICD-8). In the ICD-9, however, the category of ‘paranoid schizophrenia’ included the subtype of ‘paraphrenic schizophrenia’. In the ICD-10 the entity was included as ‘paraphrenia (late)’ in the delusional disorders group (World Health Organization, 1992).

Current terminology: International consensus

In 2000, the International Late-Onset Schizophrenia Group proposed the terms ‘late-onset schizophrenia (LOS)’ for cases with onset between 40 and 60 years and ‘very-late-onset schizophrenia-like psychosis (VLOSLP)’ for those presenting first after age 60. The panel concluded that evidence supported these age cut-offs and that these diagnoses had face validity (Howard et al., 2000). The distinction of the VLSOLP was supported by strong empirical evidence, with the LOS age criteria of 40 years more arbitrary; however, the experts felt that both had clinical usefulness and were intended to promote research in the field (Howard et al., 2000). Despite initial concerns, subsequent research has not shown a significant likelihood of affective disorders misclassified as LOS or VLOSLP. Moreover, EOS and LOS appear to be very stable diagnoses; they remained unchanged in as many as 93% of cases in a recent follow-up and only rarely were they reclassified as mood disorders (Taylor, 2001; Vahia et al., 2010). Although stronger evidence supports the distinction of VLOSLP as opposed to LOS, few studies have focused on this diagnosis specifically. In this chapter, we use the term LOS to indicate both LOS

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and VLOSLP, except where specified. We also omit use of the term 'late paraphrenia', unless specified.

Epidemiology

Poorly defined diagnostic criteria, diverse terminology, and heterogeneity of samples have limited epidemiological data on psychotic symptoms in older people.

The prevalence of paranoid ideation in individuals over age 65 has been reported to be as high as 6%, although symptoms arising in the context of cognitive impairment account for most of these cases. Forsell and Henderson (1998) found an overall prevalence of 12.1% in those with cognitive dysfunction, compared to 2.6% in those without (Christenson and Blazer, 1984). Older individuals also seem to be more susceptible to both visual and auditory hallucinations, although women appear to be the most at risk in later age than men and they experience a later peak prevalence (Tien, 1991). Rates of one-year psychotic symptom prevalence in the oldest old (over 95 years) have been estimated to be as high as 7.4%. The risk of psychosis appears directly proportional to age in the geriatric population. Van Os and colleagues (1995) suggested that incidence rates increase by 11% every 5 years after age 60. From 10 per 100,000 person-years between 60 and 65 years, the incidence rate reached 25 per 100,000 person-years in people 90 years and older. These rates reflect incidence for all nonaffective, nonorganic psychoses, including schizophrenia.

The incidence rates of schizophrenia peak between ages 16 and 25 years and then again in the 46–55 years age group, and there may in fact be a third peak in incidence rates in individuals aged 65 and older (Castle and Murray, 1993). A considerable overlap between late-onset psychosis and schizophrenia exists in epidemiologic studies. In a prospective study assessing new cases of schizophrenia fulfilling DSM-IV criteria, Mats Bogren and colleagues (2010a) found an incidence rate of 8 per 100,000 person-years in the age group of 65 + years (American Psychiatric Association, 1994). Rates of 15.6 and 17 per 100,000 person-years have been suggested for delusional disorder (based on DSM-III-R) and late-paraphrenia (as per Kay and Roth's criteria), respectively (American Psychiatric Association, 1987; Copeland et al., 1998; Holden, 1987; Kay and Roth, 1961). New onset of psychosis in late-adulthood therefore frequently occurs outside the context of schizophrenia or schizoaffective disorder. One-year prevalence rates of LOS in a Dutch catchment area of 25,600 adults aged 60 years and older was 0.14%, compared to EOS (0.35%) and VLOS (0.05%) (Meesters et al., 2012).

There is evidence that incidence rates are higher for women, and women:men ratios vary from 1.7:1 to as high as 45:2 (Bleuler, 1943; Herbert and Jacobson, 1967; Howard et al., 2000; Meesters et al., 2012). Whether gender ratios represent real differences in incidence rates based

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on true risk factors or whether they are impacted by research bias or cohort effects remains subject to debate.

In a 1997 study conducted in the UK, African-Caribbean people were underrepresented among very late-onset (first symptoms after 60 years) compared to very early-onset cases that were diagnosed before age 25 years (4% and 40%, respectively), but older adults from this ethnic background had higher incidence rates of broad schizophrenia (diagnosed 30–64 years of age) and VLOSP compared to Caucasians (Bhugra et al., 1997; Castle et al., 1997; Mitter et al., 2004; Mitter et al., 2005; Reeves et al., 2003; Reeves et al., 2001; Reeves et al., 2002).

Risk factors and correlates

As with epidemiology, the literature on LOS is limited by lack of standardization in outcomes criteria, populations, and evaluation tools, as underscored in a systematic review by Brunelle and colleagues (2011). Longitudinal studies assessing predictors of LOS are few and current knowledge relies primarily on cross-sectional data (Köhler et al., 2007).

Genetic risk

A significant family history of psychotic disorders has not been reported with LOS, although this probably reflects a lower familial burden in LOS compared to EOS rather than a complete lack of association. A wide variation can be noted in the reported prevalence rates of schizophrenia in relatives of both EOS and LOS subjects, which can be attributed to the different age cutoffs and/or diagnostic criteria used. To our knowledge, only Köhler et al. (2007) have prospectively studied the risk imparted by a positive family psychiatric history. Neither depressive nor psychotic disorders appeared to increase risk, consistent with cross-sectional evidence. Jeste and colleagues (1995) found no difference in family prevalence of depression in persons with LOS or EOS, or unaffected controls.

More recently, data from linkage-analyses seem to suggest that the age of onset is, at least in part, dependent on genetic predisposition, and that genes also have an effect on the phenotype (Hamshere et al., 2011). This may partly explain differences in clinical presentation of LOS and EOS. Several genetic risk factors have been proposed for LOS. The *DRD2* gene and specifically one of its polymorphisms, *rs2734839*, was strongly associated with older age of onset, although the number of subjects above age 40 was insufficient to draw any firm conclusions (Voisey et al., 2011). A link between the CCR5 32-bp deletion allele and LOS has also been suggested (Rasmussen et al., 2006). Dopa-decarboxylase seems to affect the age at first presentation, with certain genotypes containing the 1-bp deletion potentially increasing the likelihood of LOS in men (Borglum et al., 2001). These findings point toward a genetic susceptibility to psychosis even in late-onset cases, which could be both specific to LOS

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and shared with EOS, though the genetic susceptibility seems lower for LOS than for EOS.

Gender

The higher incidence rate of LOS in women does not necessarily imply causality. While it may indicate higher risk, other factors like access to care, proportion of individuals at risk, or even diagnostic bias may underlie this higher rate. It has been hypothesized that differences in life-expectancy between genders could also contribute to the increased incidence found in older women compared to men (Howard et al., 1994). As the gap in longevity between men and women has narrowed between 1970 and the twenty-first century, and might continue to do so over the next decades, it would be interesting to see if this is accompanied by a corresponding trend of the incidence rates for LOS to even out between both genders (Pinkhasov et al., 2010). Surprisingly, no difference in incidence rates of late-onset psychosis was found in a systematic review of longitudinal risk factors, possibly because higher incidence in women does not translate into a higher risk ratio in prospective studies (Brunelle et al., 2011). Huang and Zhang (2009) studied Taiwanese individuals older than age 60 admitted with a diagnosis of schizophrenia and reported that the difference in gender proportions was not significant between the early- and late-onset groups, women representing 44.8% and 34.7% of all cases, respectively.

Interestingly, as the familial burden of schizophrenia increases, the effect of gender on age of onset appears to lessen. Several authors have reported comparable men-to-women ratios in patients with a positive family history, even in late-onset cases (Abel et al., 2010; Leboyer et al., 1992; Rasanen et al., 2000). The observed gender differences in prevalence rates for LOS have led to the so-called oestrogen hypothesis of schizophrenia—the onset of symptoms in older women due to the loss of the previous protection conferred by the oestrogenic influence (Häfner et al., 1998; Seeman and Lang, 1990). Oestrogen modulates several neurotransmitter systems, including the dopaminergic, serotonergic, GABA-ergic, noradrenergic, and cholinergic pathways, all of which have been implicated in psychotic disorders (Behl et al., 1995; Brann et al., 2007; Kölsch and Rao, 2002; Lee and McEwen, 2001). However, attempts to identify specific polymorphisms of the oestrogen receptors responsible for schizophrenia or LOS have been mostly inconclusive, and there are currently no data supporting the hypothesis that a genetic variant would have a specific influence on age of onset other than through the general mechanisms (Ouyang et al., 2001). Using first admissions data for VLOSLP, Reeves and colleagues (2002) found that male patients were significantly more likely to be lost at follow-up, which points to differences in help-seeking behaviours between genders.

In summary, the question of whether female gender is itself a significant risk factor for the development of LOS is not fully understood yet, but women constitute a higher proportion of the clinical population. However,

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gender does not seem to exert any direct effect outside its association with age at onset (Häfner, 2003; Häfner et al., 1998; Leboyer et al., 1992).

Sensory loss/medical comorbidity

Sensory loss has been consistently implicated in the development of late-life psychosis since an association with hearing loss was reported for the first time by Kay and Roth (Kay and Roth, 1961; Roth, 1955). Symptoms of paranoia following experimentally induced deafness have been described and the literature suggests that adjustments to hearing aids can lead to the resolution of symptoms (Eastwood et al., 1981; Khan et al., 1988; Zimbardo et al., 1981). Authors have reported that hearing loss in those cases is more often conductive and usually severe, bilateral, and appearing early in life (Cooper, 1976; Cooper and Curry, 1976; Cooper et al., 1974; Prager and Jeste, 1993). The association between schizophrenia and hearing impairment appears stronger for VLOSLP than for LOS, but these associations have not been confirmed in longitudinal studies. Less convincing evidence exists for an association with visual deficits (Howard et al., 2000), though prospective studies have demonstrated that people with visual deficits are at significantly increased risk of psychosis, although it has not been demonstrated specifically for LOS (Blazer et al., 1996; Forsell, 2000; Köhler et al., 2007).

Although the existing evidence suggests a correlation, specific aetiological pathways linking sensory deficit and psychosis have been disputed. Proposed theories include sensory loss, reinforcing premorbid tendencies toward isolation (Corbin and Eastwood, 1986), or that persons with sensory loss would simply be less likely to seek treatment.

Comparing patients with early- vs very-late-onset, Rodriguez-Ferrera and colleagues (2004) obtained a higher than expected prevalence of hearing loss in their very-late-onset group (54%), with only 15% in the younger onset group including cases of EOS and LOS, with a mean age of onset of 36 years (SD = 11.3). Almeida and colleagues (1992) reported very similar rates of 41% and 6.6% for LOS and EOS, respectively. Reported prevalence rates of hearing deficits in the literature in the general older population range between 25% and 80% (Newman and Sandridge, 2004). A recent review suggested that hearing deficits severe enough to impair conversation affect approximately 10% of the general population and as many as 40% of adults over age 65, with 80% of all cases of hearing loss occurring in older people (Huang and Tang, 2010). In light of these numbers, the high frequency of hearing impairments in patients with VLOSLP and to a lesser extent LOS is hardly surprising.

There is very limited literature on medical comorbidity in people with LOS, especially considering the significant burden of medical issues in the older population in general and in the psychiatric population in particular. Indeed, some 'geriatric syndromes' are specific to this group, which is also at higher risk of accumulating concurrent medical illnesses, with resulting adverse effect on functional and cognitive status. At least 20–30% of people over 65 years of age are believed to suffer from chronic

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diseases (De Luca d'Alessandro et al., 2011). Moreover, medical issues are often overlooked in this population. Data from a chart review of 79 consecutive geriatric psychiatry hospital admissions (University of California, San Diego, Senior Behavioral Health Unit) indicate that 34% of the patients had unrecognized medical conditions (Woo et al., 2003).

An association between occlusive carotid and vertebral arteries disease and late-onset of psychiatric disorders has been reported and cardiovascular risk factors seem to be increased in subjects with LOS, but also late-onset affective disorders (van der Heijden et al., 2010). Barak and colleagues (2002) indicated that medical comorbidities were frequent in both groups of older people with either VLOSLP or chronic schizophrenia (71.4% vs 57.1%, respectively, although it was not significant), with hypertension being the most frequent medical condition, followed by ischaemic heart disease and diabetes. The rates of medical comorbidities seem to be higher in late-onset delusional disorder than schizophrenia, with also more neurological conditions in the first group (Riecher-Rössler et al., 2003). Evidence for potential medical risk factors from longitudinal studies is limited. Henderson and colleagues (1998) found that current physical symptoms increased the risk of delusions and hallucinations, although causality was not established for past physical illnesses. There is a dearth of data about the topic of a history of obstetric or perinatal complications in LOS patients. To our knowledge, only one longitudinal study has been published discussing the rates of perinatal complications in LOS, retrospectively looking at a small sample of 12 LOS patients and concluding against any predisposing effect (Castle et al., 1997; Reulbach et al., 2007).

Cognitive patterns and psychopathology

Cognitive patterns and psychological mechanisms have been discussed extensively in the general literature on LOS. 'Theory of mind', 'mentalization', and 'social cognition' are related concepts that describe the processes used by human beings to make sense of their environment and interact with others. It has been proposed that decreased social exploration is an expected phenomenon with normal ageing and that its interaction with cognitive impairment could increase the susceptibility to psychotic symptoms in people with otherwise healthy development and mentalization patterns. Similar to what has been reported for EOS patients, those with LOS have been found to make significantly more mentalizing errors on testing than older controls, but they did not demonstrate the impaired performance in probabilistic reasoning and exaggeration in self-attribution bias typical of the early-onset individuals (Moore et al., 2006). The literature on social cognition has been burgeoning over the last years in the field of schizophrenia in general, and the extent of the deficits appears to mirror those in neurocognition; whether this will prove relevant in the LOS population remains to be determined (Hofer et al., 2010). Fromholt and colleagues (1999) described the psychological characteristics of 20 individuals with late paraphrenia and found that the subjects' emotional reactions and coping

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mechanisms appeared congruent to their subjective views of the problem. That is, their reactions would have been deemed rational or logical if the patients' perceptions corresponded to the reality. This was replicated in a later study by Quin and colleagues (2009). Fromholt and colleagues (1999) also noted that in all but one patient the delusional ideas were plausible, i.e. they 'did not violate physical laws or include references to any supernatural phenomena'. One study found that EOS patients had significantly lower scores on the Hinting Task, a measure of Theory of Mind abilities, compared to age-comparable LOS patients and controls, after adjusting for educational achievement (Smeets-Janssen et al., 2013). The authors proposed that better Theory of Mind functioning might be protective and delay the age of onset of schizophrenia.

In the historical literature on social tendencies and LOS, there are contradictions. While the late paraphrenia described by Roth has been thought to occur mostly in older women with a lifelong tendency toward solitariness and suspiciousness, Janzarik's 'Kontaktmangelparanoid' was described in women with a previously high level of vitality and poor tolerance to solitude who found themselves newly isolated by factors inherent to the ageing process (Janzarik, 1957, 1973; Kojo, 2010; Roth, 1955). In most cases, a progressive deterioration in social networks often prefigured the onset of psychosis and initiated a process of 'life-review' in which subjects reminisced over hostile relationships with some family members, expressed regrets for past actions, and described well-established patterns of solitary coping styles that could be related to the perception of having always been different or 'outsiders' as described by most patients (Quin et al., 2009). Whether they might be the origin or a consequence of LOS remains unclear. Comparing older people with late-onset of depression or schizophrenia and unaffected age-matched controls, Giblin and colleagues (2004) demonstrated that LOS patients had significantly higher scores in the following domains on the Schema Questionnaire: 'rejection and disconnection', 'impaired autonomy and performance', 'other-directedness', and 'over vigilance and inhibition'. They were also more likely to have a low morale about the ageing process, even compared to those with major depression. However, they had the highest severity of current depressive symptoms, which could have introduced a significant recall bias (Schmidt et al., 1995). Contrary to these findings, there is evidence pointing toward a lack of aetiological association between depressive schemas and LOS. Indeed, McCulloch and colleagues (2006) found that not only was there no indication of depressive cognition or self-conception in individuals with late-onset psychosis, but also there was nothing to suggest changes over time; hence the possible contribution of depression to the onset of symptoms was limited.

Unfortunately, to our knowledge only two groups have assessed this topic longitudinally. Köhler and colleagues (2007) found that lifetime depressive symptoms at baseline were not associated with the onset of psychosis (not restricted to schizophrenia) in individuals over age 50,

despite a significant effect in younger cohorts. Interestingly, although there was a trend toward lower influence with older age of onset, 'neuroticism' retained its significance as a contributive factor in late-onset psychosis. This is congruent with the analysis from Bogren and colleagues (2010b) of premorbid behavioural and personality-related signs and symptoms predictive of psychosis, with only the two clusters 'nervous-tense' and 'abnormal-antisocial' reaching significance for schizophrenia. The description of the latter cluster indicates what would now be more suggestive of cluster A personality disorders.

Abnormal premorbid personality traits have often been implicated. Fuchs (1999b) found high rates of personality pathology in a sample of 38 late paraphrenia patients and indicated that 39% had met the criteria for paranoid or schizoid personality disorders prior to the psychosis, and the frequency of characteristic traits has been reported to be as high as 70% in older literature. Subjects affected by late-onset psychotic disorders have been described by early British authors as 'suspicious', 'quarrelsome', 'hostile', 'sensitive', 'unsociable', 'reticent', 'odd', 'eccentric', 'histrionic', 'pretentious', and exhibiting a long-standing difficulty to establish or maintain intimate relationships (Giblin et al., 2004; Herbert and Jacobson, 1967; Howard et al., 1994; Kay and Roth, 1961; Post, 1966). In LOS specifically, Pearlson and colleagues (1989) noted patterns of having been 'reclusive and introverted', with 'few friends, poor interpersonal relationships and peculiar religious beliefs'. Brodaty and colleagues (1999) described persons with LOS as 'odd and eccentric', 'suspicious and detached' compared to normal controls, and similar to previously described traits in late paraphrenia. Longitudinally, no premorbid condition has been clearly associated with the onset of psychotic symptoms; anxious manifestations may potentially be predisposing and a prior diagnosis of post-traumatic stress disorder had been given to several LOS patients with significant childhood trauma (Reulbach et al., 2007; Sachdev et al., 2000; Tien and Eaton, 1992). Although substance-related disorders are more common in older people with schizophrenia than without, LOS specifically has not been well studied (Jeste et al., 1996; Mulsant et al., 1993). Reviews of the longitudinal studies were inconclusive (Brunelle et al., 2011; Köhler et al., 2007; Tien and Eaton, 1992; Wiles et al., 2006).

Pathophysiologic processes

Sociodemographic factors

Some sociodemographic characteristics of the subjects affected by LOS are likely not predisposing factors and reflect the direct consequences of later age of onset. However, they are important to the understanding of the pathogenesis of schizophrenia in late life, and are mentioned here.

Studies consistently show that subjects with LOS may have similar marriage rates as normal controls (especially for VLOSLP) and are much more likely to be, currently or formerly, married than their earlier-onset

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counterparts (Barak et al., 2002; Girard and Simard, 2008; Hassett, 2002). It has also been suggested that they might have higher rates of divorce (or initiating the divorce) and widowhood (Almeida et al., 1992; Rees, 1971; Fuchs, 1999b; Girard and Simard, 2008; Herbert and Jacobson, 1967; Howard et al., 1994; Jeste et al., 1995; Kay and Roth, 1961). One exception emerged from a comparison of EOS and LOS in chronically hospitalized patients in Taiwan, with high rates of marriage in both groups, possibly corresponding to a cultural phenomenon (Huang and Zhang, 2009). Compared to those with early-onset, patients with LOS might have fewer friends and fewer children than normal controls (Barak et al., 2002; Brodaty et al., 1999; Gurian et al., 1992; McCulloch et al., 2006; Rodriguez-Ferrera et al., 2004; Romero-Rubiales et al., 2004; Semple et al., 1997).

While an association with academic achievement remains unclear, better work performance and employment history reflected a much better level of premorbid adjustment for schizophrenia patients diagnosed later in life (Barak et al., 2002; Castle et al., 1997; Fuchs, 1999b; Girard and Simard, 2008; Girard et al., 2011; Jeste et al., 1995; Vahia et al., 2010). These findings, however, have not been replicated in longitudinal studies (Brunelle et al., 2011). Functional limitations have not been studied in relation to schizophrenia and there is inconsistent evidence as to whether they increase the risk of psychosis in older people directly (Blazer et al., 1996; Forsell, 2000). Although there are very limited data on this topic, it is possible that an urban status at birth might predispose to LOS, as has been suggested already for EOS (Marcelis et al., 1998).

Adverse life events

Negative experiences early in life can affect developmental tasks and thereby increase susceptibility to psychosis when they occur early in life, but psychosocial stressors may exert a larger impact on the psychotic episode's development. Both have been described in relation to LOS, although the specificity and wide range of adverse events described in the literature likely impairs generalization. Results from a systematic review of longitudinal studies on LOS indicated that both the number and intensity of negative life events can contribute to the onset of psychotic symptoms later in life, and exposure to the Holocaust has been implicated for schizophrenia specifically (Brunelle et al., 2011; Reulbach et al., 2007). Childhood traumas and experiences perceived as discriminating, humiliating, or threatening have been frequently identified in subjects with LOS (Fuchs, 1994, 1999a,b; Gurian et al., 1992; Rockwell et al., 1994). For those with EOS, early life events have not been associated with the persistence of psychotic symptoms in older age, but the accumulation of stressors throughout the lifetime has been implicated (Cohen et al., 2011). Psychosocial adversity can play a role during adulthood as well, and certain ethnic groups such as African-Americans have been diagnosed more frequently. While diagnostic bias, perceived discrimination, and stress related to the migration have been implicated for these associations, none has emerged as a significant predisposing

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factor in longitudinal evidence (Blazer et al., 1996; Brunelle et al., 2011; Forsell, 2000; Forsell and Henderson, 1998; Mitter et al., 2005; Mitter et al., 2004; Reeves et al., 2003; Reeves et al., 2001). In a recent article on LOS from Japan, psychosocial stresses were deemed causally related in 65.8% of the cases, and in 36% of those the subjects reported a sense of loss. Similar associations with acute stresses or losses have been reported in other studies (Rees, 1971; Fromholt et al., 1999; Janzarik, 1973; Kay and Roth, 1961; Yasuda and Kato, 2009). This is compatible with the view of LOS and EOS as unique single disorders, with LOS manifesting later in more resilient individuals (Schmid et al., 2011).

Neuropathology

Neuropathological mechanisms remain central to contemporary conceptualizations of schizophrenia, including: i) dysfunction of the neurotransmitter pathways in the central nervous system, primarily implicating dopamine, glutamate, and serotonin; ii) neurodevelopmental alterations, suggested by regional brain abnormalities on both structural and functional imaging; and iii) modifications at the cellular level, with a postulated reduction in oligodendrocytes and/or aberrant neuronal cytoarchitecture (Pickard, 2011). However, the extent to which these processes contribute specifically to illness manifestation in late life and the role of alternative mechanisms is not well understood.

The first brain imaging study of the late-onset population was published by Haug (1962) involving seven patients with a first episode of 'psychosis' after the age of 45 years. Using the technique of pneumoencephalography, he reported evidence of cerebral atrophy and dilated ventricles. It took almost a twenty-five years for the next study reporting on brain imaging in patients with LOS, when Miller and colleagues (1986) reported computer tomography (CT) results on a small sample of five women with late paraphrenia, and noted that three had cortical or subcortical changes and another showed signs of normal pressure hydrocephalus. Several subsequent studies all determined that ventricle-to-brain ratios (VBRs) were larger in the patients than the normal controls group (Naguib and Levy, 1987; Pearlson and Rabins, 1988; Rabins et al., 1987). More recent investigations have mostly used magnetic resonance imaging (MRI) techniques, in an attempt to assess periventricular and deep white matter changes better. The first two studies (Breitner et al., 1990; Miller et al., 1989) described the MRIs of subjects with a broader diagnosis of 'late-life psychosis' or 'late-onset paranoid illness'. In the first study, 20% of them had evidence of 'silent vascular disease' and tumours were discovered in another 12%. The second group reported vascular lesions in the pons or medulla of seven out of eight subjects, but none in normal controls. Miller and colleagues (1991) later wrote that white matter lesions affected 42% of subjects, presenting with first onset of 'psychosis' after age 45, as opposed to only 8% of the age-matched healthy comparison subjects, predominantly in the

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temporal and frontal lobes. However, no definite pattern of white matter lesions has been established.

A literature review published in 2010 suggested that extracranial arterial pathology also contributed to the development of LOS. A significantly higher burden of premorbid cardiovascular risk factors was described in those with late-onset psychiatric disorders, including schizophrenia (van der Heijden et al., 2010). It is possible that this finding reflects a distinction between LOS and VLOSLP.

Volumetric studies have failed to pinpoint any abnormality specific to late-onset patients and findings are mostly concordant to those with EOS. The only notable difference was the larger thalamic volumes found in patients with LOS compared to their early-onset counterparts (Barta et al., 1997; Corey-Bloom et al., 1995; Rabins et al., 2000; Sachdev and Brodaty, 1999b; Sachdev et al., 2000; Sachdev et al., 1999; Sachdev and Brodaty, 1999a; Symonds et al., 1997). One recent study showed larger gray matter volumes in the left precuneus of LOS patients compared to EOS patients and non-psychiatric controls (Egashira et al., 2014). However, there have been no demonstrated alterations in the size of the frontal lobes, hippocampus, parahippocampus, thalamus, or basal ganglia structures in patients with LOS compared to older controls (Howard et al., 1995). Sachdev and colleagues (2000) later confirmed that the hippocampus and amygdala volumes in older people with LOS and EOS were comparable and were not significantly associated with their cognitive performances.

Diffusion tensor imaging (DTI) results have confirmed the integrity of frontal lobes and frontal cortical tracts, which had already been suggested by volumetric studies (Jones et al., 2005). However, studies using single photon emission tomography (SPECT) have suggested that up to 83% of LOS patients suffered from frontal or temporal hypoperfusion. In one study, the regional cerebral blood flow of patients with LOS showed a different pattern of alteration than that of subjects with EOS. Reduced blood flow was observed bilaterally in the postcentral gyrus for LOS patients, while the precentral and inferior frontal gyri were more affected in the EOS group. It was postulated that these changes were more likely attributable to the age of onset rather than the chronological age of the subjects (Wake et al., 2011; Wake et al., 2016). One case study found resolution of differential blood flow in the striatum and thalamus compared to the left frontal and temporal cortex after successful treatment for VLOS with catatonia (Tsujino et al., 2011).

Lohr and colleagues (1997) reported a significant difference in the frequency of minor physical anomalies in those two sets of patients. While the subjects with Alzheimer's dementia did not differ from normal controls, older people with LOS or EOS, as well as those with unipolar depression, all had more anomalies. Pathological examinations have been rarely reported, but the absence of Alzheimer's disease as defined by extensive neurofibrillary tangles seems to be consistent (Bozikas et al.,

2002; Casanova et al., 2002). Although the proportion of tangles was not abnormal, other neuritic changes have been observed. On the basis of their studies, Casanova and colleagues have proposed the concept of a 'restricted limbic tauopathy' that affects LOS and, to some extent, EOS patients (Casanova et al., 2002; Casanova and Lindzen, 2003). In patients with schizophrenia, the familial loading for Alzheimer's, vascular, or Lewy body dementias has not been found to be higher in those with a later compared to an earlier onset of symptoms (Brodaty et al., 1999; Howard et al., 1997). From a systematic review of the longitudinal studies on the risk factors for late-onset psychosis, cognitive impairment not reaching the threshold for dementia emerged as a probable predictor for psychotic symptoms at follow-up, but not for schizophrenia per se (Brunelle et al., 2011; Forsell, 2000; Henderson et al., 1998; Tien and Eaton, 1992). The Wechsler Adult Intelligence Scale-Revised (WAIS-R) similarities subtest and the California Verbal Learning Test (short- and long-delay free recall) may be the two most sensitive neuropsychological measures discriminating between LOS and Alzheimer's disease in patients already diagnosed with LOS or VLOSLP (Girard et al., 2011; Zakzanis et al., 2003). However, neuropsychological testing in individuals without psychosis was not shown to have any predictive value regarding the likelihood of subsequently exhibiting schizophrenia manifestations (Blazer et al., 1996; Henderson et al., 1998).

In summary, LOS does not appear to be related to Alzheimer's disease or other dementia pathology. However, it is still unclear whether a neurodegenerative process is at play in this condition, mainly because of the lack of distinction in the literature between cases of LOS and VLOSLP and the pooling of various psychotic disorders together in studies. Current evidence indicates that VLOSLP might be more associated with a neurodegenerative disease, while LOS is more aetiologically similar to EOS, although this is not completely clear.

Inflammation

A number of studies have reported elevated levels of inflammatory markers and oxidative stress markers in schizophrenia, though few studies have examined inflammatory markers specifically in LOS (Joseph et al., 2015; Lee et al., 2016a,b). In 2014, Wium-Andersen and colleagues (2014) reported that elevated levels of C-reactive protein (CRP), a biomarker of systemic inflammation, were associated with a six- to 11-fold increased risk for LOS and VLOS based on a 20-year longitudinal Danish cohort study of over 78,000 individuals. Mean CRP levels were higher for persons with schizophrenia (EOS and LOS subtypes) compared to those without schizophrenia, even when adjusting for age and gender. This was the first study examining a large cohort for LOS and VLOS in regards to inflammatory markers.

Clinical features

Late-onset schizophrenia

Positive and negative symptoms

The conclusions of the International Consensus on Late-Onset Schizophrenia Group pointed toward greater similarities than differences in the clinical presentation of schizophrenia arising in early and late life, especially regarding the positive symptomatology and between ages 40 and 60 years. However, in clinical samples, cases with very late onset were associated with a low prevalence of formal thought disorder and affective blunting and a higher prevalence of visual hallucinations (Grahame, 1984; Howard et al., 1993; Howard et al., 2000; Jeste et al., 1995; Jeste et al., 1997; Kay and Roth, 1961; Pearlson et al., 1989; Post, 1966).

Whether LOS patients experience more severe positive symptoms overall compared to those with early-onset is not fully clear. Yasuda and Kato (2009) found that the paranoid subtype applied to over one-half of their LOS sample and was significantly higher than in the older group with earlier onset. Mason and colleagues (2013) reported similar findings of increased paranoia in the LOS group, however the differences dissipated when the analysis matched for age (Mason et al., 2013). On the other hand, Vahia and colleagues (2010) suggested similar rates for the early- and late-onset groups, although positive symptoms were less severe overall among those with LOS. The absence of significant difference in positive symptomatology has been replicated in other studies (Hanssen et al., 2015; Huang and Zhang, 2009; Jeste et al., 1995; Pearlson et al., 1989; Rodriguez-Ferrera et al., 2004). Some specific features do appear to be more common in the LOS population, such as persecutory, elaborate, and systematized delusions. Delusions and hallucinations may become more prevalent with older age rather than with older age of onset, but delusions of partition or 'the belief that people, objects or radiation can pass through what would normally constitute a barrier to such passage' are especially frequent in those with LOS and much rarer in older and young EOS patients (Howard, 2006; Howard et al., 1992). Individuals with a later onset are also more susceptible to experience visual, olfactory, or tactile hallucinations and in several sensory modalities simultaneously (Alici-Evcimen et al., 2003; Castle et al., 1997; Girard and Simard, 2008; Howard et al., 1993; Pearlson et al., 1989; Sato et al., 2004; Wynn Owen and Castle, 1999).

It has been increasingly recognized that a later onset might not be as protective as originally assumed, with recent evidence suggesting comparable severities of negative symptoms in EOS and LOS and even in VLOSLP (Girard and Simard, 2008; Jeste et al., 1995; Vahia et al., 2010). Indeed, VLOSLP seems to be characterized by prominent positive symptoms but not less negative symptomatology than LOS, although it is rarely specifically assessed on its own. The level of psychomotor activity appears to distinguish the two conditions, with LOS patients presenting with more apathy and abnormal psychomotor activity (Barak et al., 2002; Girard and Simard, 2008).

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Cognition

Cognitive changes are among the cardinal features of schizophrenia, regardless of age of onset, and had been under consideration for inclusion as a distinct dimension in the DSM-5 section on schizophrenia—though ultimately they were not included (Bora et al., 2010; Keefe and Fenton, 2007; Laughren, 2011).

Consistent with the overall literature on schizophrenia, late-onset patients were found to have lower cognitive performance than normal controls. Ting and colleagues (2010) reported that LOS patients were more impaired than age-matched controls on most cognitive tests, with the exception of those for the recall of newly learned verbal information (using the California Verbal Learning Test: Woods et al., 2006). However, those with LOS outperformed patients with Alzheimer's disease on every measure, including retrieval, the only notable exception being a nonsignificant difference in learning new verbal material. These more recent findings are very similar to the first neuropsychological descriptions of LOS patients, attributed to Hopkins and Roth in 1953. Comparing older subjects belonging to several different diagnostic categories, they reported that those with late paraphrenia had a much better performance on all tests than those with dementia. The severity of impairments was similar in late paraphrenia and affective patients, but the two groups showed distinct patterns on neuropsychological assessment (Hopkins and Roth, 1953). One longitudinal study found no difference in risk of developing dementia between patients with LOS and late-life depression (Rabins and Lavrisha, 2003).

Rajji and colleagues (2009) conducted a meta-analysis on cognitive deficits found in subjects with a first-episode in adult life, youth-onset, or LOS. From the nine studies selected, the authors concluded that LOS patients have an overall better cognitive performance than those with youth-onset or first-episode schizophrenia, though the patterns of cognitive deficits differ in each group. The LOS patients had more impairment on measures of attention, fluency, global cognition, IQ, and visuospatial construction than the other two subgroups, while arithmetic, digit symbol coding, and vocabulary were mostly preserved. Similarly, a study of LOS patients, EOS patients matched for duration of illness, and age-matched controls showed that LOS patients had intermediate memory performance—better than the EOS patients but worse than the controls (Brichant-Petitjean et al., 2013). This challenges the assumption of minimal differences in the cognitive functioning of patients with EOS and LOS (Heaton et al., 1994; Jeste et al., 1995; Sachdev et al., 1999). It is possible that this design allowed for the detection of results that did not reach significance in isolated studies because of small sample sizes; but it might also reflect the patient groups in the analysed studies. Unfortunately, in most studies, older adults with LOS are compared to older adults with EOS. It has been suggested that the younger the age of onset, the greater the severity of cognitive and functional impairments; however, while chronicity contributes significantly to the cognition

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scores, it has not been shown to alter the effect of age of onset on specific measures. LOS subjects most consistently perform better on measures of abstraction/flexibility, semantic/verbal memory, and learning. These findings have been replicated by other authors, although some also noted lesser impairment in processing speed for the late-onset group (Girard et al., 2011; Jeste et al., 1997; Tuulio-Henriksson et al., 2004; Vahia et al., 2010).

Comparisons of executive functions in LOS and EOS are inconsistent and the current consensus is that impairments are manifest regardless of age of onset (Rajji and Mulsant, 2008). A positive correlation exists between family history of schizophrenia, younger age of onset, and poorer cognitive performance, although familial loading might not have such a significant effect in late-onset cases. How this contributes to the neurocognitive features in LOS has, however, not been well studied (Goldberg et al., 2011; Tuulio-Henriksson et al., 2004). One 2015 study found no significant neuropsychological differences between LOS and VLOSLP, when controlling for age (Hanssen et al., 2015).

Mood

Compared to normal controls, patients with LOS appear to endorse a higher level of depressive symptoms (Jeste et al., 1995; Moore et al., 2006). However, there was no evidence of depression in the LOS group in a study by McCulloch and colleagues (2006) comparing LOS patients to depression patients and healthy controls; both LOS and normal subjects exhibited a better self-esteem than the depressed individuals. When comparing with older EOS patients, Jeste and colleagues (1995) found no significant between-group differences, and a study by Rodriguez-Ferrera and colleagues (2004) showed a trend toward higher depression levels in EOS, though significance was not reported.

Differential diagnoses of psychotic symptoms in older people

Several conditions can present with psychotic symptoms in older patients. A detailed discussion of all possible causes is beyond the scope of this section, but we summarize the major differential diagnoses.

Early-onset schizophrenia

Table 43.1 provides a summary of the differences between EOS and LOS. Recent studies suggest that LOS is likely a distinct subtype of schizophrenia due to psychopathological and mechanistic differences from EOS (Maglione et al., 2014).

Late-onset schizophrenia

Table 43.1 Characteristics of various types of late-life psychosis.

	EOS	LOS	VLOSLP	PoD
Family history of schizophrenia	+	+	-	-
Female preponderance	-	+	++	-
Minor physical anomalies	+	+	-	-
Specific brain abnormalities (MRI)	-	-	+	+/-
Dementia-like cognitive decline	-	-	+	++
Magnitude of cognitive impairment	+	+	++	+++
Paranoid subtype	+	++	+++?	N/A
Visual vs auditory hallucinations	+/-	+	+	++
Complex vs simple delusions	++	+	+	+/-

Late-onset schizophrenia

Thought disorder	+/++	+	-	-
Negative symptoms	++	+	-	-
Required neuroleptic dose	++	+	+	+/-

EOS, early-onset schizophrenia; LOS, late-onset schizophrenia; MRI, magnetic resonance imaging; N/A, not applicable; PoD, psychosis of dementia; VLOSLP, very-late-onset schizophrenia-like psychosis; +, moderately present; ++, strongly present; +++ very strongly present; -, not likely to be present; ?, only partially supported by the literature.

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Late-onset schizophrenia

Delusional disorder and other primary psychoses

Significant overlap exists between LOS, delusional disorder (DD), and late paraphrenia, to the extent that authors have challenged the validity of any diagnostic division (Howard et al., 1994; Jørgensen and Munk-Jørgensen, 1985). Riecher-Rössler and colleagues (2003) proposed that 'since clear and aetiologically meaningful differentiation between these diagnostic categories is not possible, they should not be separated by artificial diagnostic criteria for research purposes'. However, other authors have reported some evidence to support the clinical distinction of DD from schizophrenia with onset after age 40 (Evans et al., 1996). A diagnosis of DD is more often seen in older patients and is not an uncommon expression of psychosis in this population. For example, Alici-Evcimen and colleagues (2003) described 27 cases of late-onset psychosis in the 420 inpatients admitted to the sole geriatric psychiatry unit of a Turkish hospital between 1993 and 2002. From those 27 patients, five had EOS. Eight were diagnosed as having LOS, six with VLOS, and eight had DD. In a study of older people with schizophrenia, it was found that 27% of those diagnosed after age 60 met the criteria for DD, as opposed to none in the early-onset group (Rodriguez-Ferrera et al., 2004). In fact, diagnostic classification seems to rely heavily on age. Results from another group suggest that age accounted for 22% of the variation in the two diagnoses of schizophrenia and DD (Riecher-Rössler et al., 2003).

Schizophreniform disorder resembles schizophrenia, but lasts less than six months. Older patients with this disorder often demonstrated good premorbid adaptation, and the sudden onset of florid psychotic symptoms generally leaves them perplexed and confused. The episode might end as abruptly as it had begun, often with a return to the premorbid level of functioning (Jørgensen et al., 1997).

Schizoaffective illness in older patients has not been well described, probably because it is often included with cases of LOS. Among 27 very-late-onset psychosis cases described by Rodriguez-Ferrera and colleagues (2004), two received a diagnosis of schizoaffective disorder. Holden (1987) did describe a schizoaffective subtype of late paraphrenia associated with a high prevalence of auditory hallucinations but almost no visual manifestations. Affected patients had low rates of psychiatric antecedents and sensory deficits and were most likely to be alive at ten years compared to the other subgroups.

Isolated hallucinations can be found in visually impaired individuals (Schadlu et al., 2009). They have been described as a commonly occurring phenomenon in persons who have experienced widowhood, described in approximately 4% of widowers (Rees, 1971; Khouzam et al., 2005).

Delusions of misidentification, e.g. the Capgras syndrome, might occur in people with primary psychotic disorders but should herald the possibility of an underlying organic condition. They are relatively common in

Late-onset schizophrenia

Alzheimer's dementia and other neurological or medical conditions (Khouzam et al., 2005). Paranoid personality can increase the risk of late-life psychosis, but premorbid suspiciousness can also worsen with age (Manford and Andermann, 1998; Paulsen et al., 2000).

Affective disorders

Psychosis is an especially frequent accompanying feature to depressive episodes in later life. Delusions or hallucinations are mood-congruent in the majority of the cases and somatic manifestations are especially common (Jørgensen et al., 1997; Khouzam et al., 2005).

Grandiose delusions commonly appear during manic episodes. Although mania tends to emerge as an early feature in the course of bipolar disorder, it can occur for the first time in late life or can reappear as a consequence of medication changes. Mania in older people should be differentiated from frontotemporal dementia (Almeida et al., 1992; Sajatovic and Chen, 2011).

Delirium and substance-induced psychotic disorders

While substance use disorders are comparatively less common in the older population, they are still observed with some frequency. Also, older adults are at risk for withdrawal due to sudden lack of access because of financial, mobility-related, or medical conditions. Alcohol and benzodiazepines are associated with especially high risk of psychotic phenomena during both intoxication and withdrawal and their use is not uncommon (American Psychiatric Association, 2000; Blazer and Wu, 2011; Khouzam et al., 2005). Delirium from any cause should also be suspected in first onset of psychosis and behavioural disturbances in late life (Reeves and Brister, 2008).

Dementia

Psychotic manifestations, especially visual hallucinations, can present in virtually every type of dementia and occur in up to 50% of patients at some point over the course of the illness. They are a characteristic feature of Lewy body dementia. Certain gene mutations such as progranulin (*PGRN*) and *C9ORF72* have been associated with hallucinations and psychosis in patients with frontotemporal dementia (Le Ber et al., 2008; Snowden et al., 2012). Also, people with dementia are especially vulnerable to anticholinergic side effects of medications and the resulting delirium. Psychosis can be a poor prognostic marker in this population, where antipsychotic treatment is associated with an increased mortality rate (American Psychiatric Association, 2000; Hardy, 2003; Kales et al., 2007; Paulsen et al., 2000).

Management

Late-onset schizophrenia

Clinical evaluation

The evaluation of older people presenting with schizophrenia manifestations requires assessment similar to that for any psychiatric illness in late life. Extra focus should be given to collateral information, owing to the high risk of guardedness and poor insight due to psychosis and cognitive impairment. It is also important to assess the impact of the disease on the social network. Assessment of safety includes ruling out the risk of violence toward others, even though this is reportedly more common in younger rather than older adults (Martínez-Martín et al., 2011).

The pharmacological history should focus on potentially contributing medications, including over-the-counter, herbal remedies, interactions, recent changes, and medication adherence (e.g. anticholinergic medications are often implicated as a cause of psychotic symptoms in older adults). Sexual and substance use histories should be gathered considering the risk of intoxication, withdrawal, neoplastic lesions, and sexually transmitted diseases. A complete review of personal and familial antecedents, both medical and psychiatric, with a specific focus on psychotic and neurodegenerative disorders, is mandated and should include a discussion of the premorbid level of functioning. Information should be obtained on the current pattern of impairment, course of symptoms, and accompanying physical or psychological manifestations. During physical examination, the clinician should look for evidence of neglect, abuse, decreased hygiene, incontinence, or cachexia, as well as for any sign of delirium or any indication of its aetiology. Neurological assessment should rule out increased intracranial pressure, localizing lesions, or neurodegenerative conditions like Huntington's and Parkinson's disease or Lewy body dementia, lesions of the basal ganglia or cerebellum, or seizures. A basic cognitive evaluation is mandated in all patients and should be repeated over time to rule out fluctuations in the context of delirium.

A basic work-up should consist of a complete blood count, blood chemistry profile (glucose, electrolytes with calcium and magnesium, blood urea nitrogen, creatinine, and liver function tests), urinalysis (and urine culture, if indicated), thyroid function studies, toxicology screening, vitamin B₁₂ and folate levels, and serological tests for syphilis. Brain imaging is recommended, especially for cases with acute deterioration, altered consciousness, or abnormalities on neurological examination. Some authors also present evidence for electrocardiography and routine chest radiography (Boyce, 2008; Howard et al., 2000; Reeves and Brister, 2008). It may be useful to obtain a baseline lipid panel, weight, height, and waist circumference before an antipsychotic trial, in order to monitor metabolic side effects.

Ancillary investigations should focus on ruling out other suspected aetiology based on the history and physical examination. The decision to

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perform comprehensive neuropsychological evaluation should be guided by clinical judgment, especially in settings with limited resources.

Pharmacology

Antipsychotics

No pharmacologic treatment guidelines for LOS have been established to date, mostly due to the limited evidence in this specific population. The bulk of the literature in this regard pertains to older patients with chronic schizophrenia; moreover, studies on the late-onset population usually failed to distinguish between LOS and VLOSLP. Arunpongpaissal and colleagues (2003) published a Cochrane systematic review on antipsychotic drugs use in older people with LOS, and revised it in 2012. While the 2003 search found no randomized controlled trials meeting their inclusion criteria and upon which to base any guidelines, the 2012 review identified a single randomized controlled trial of risperidone and olanzapine that was of acceptable quality (Essali and Ali, 2012). Due to the paucity of published trials, clinicians must for now use 'clinical judgment and habit to guide prescribing' (Arunpongpaissal et al., 2003; Essali and Ali, 2012). However, a more recently published study by Jin and colleagues (2013), which specifically studied older adults on antipsychotic medications, found that quetiapine may have the highest incidence of adverse events. The study also noted that older adults on antipsychotics had high discontinuation rates, limited improvement in psychotic symptoms and a 36% incidence of metabolic syndrome (Jin et al., 2013).

Atypical antipsychotics are now favoured, mainly because of the propensity of first-generation neuroleptics to induce extrapyramidal symptoms (EPS) and tardive dyskinesia (TD), to which older individuals are more prone. Benefits have been observed in older patients initially treated with risperidone or olanzapine after the switch from a typical antipsychotic (Jeste et al., 1999a,b; Ritchie et al., 2003; Ritchie et al., 2006). In older people, as many as 2–30% of patients per year may develop TD with typical antipsychotics and they are also less likely to experience remission compared to younger individuals. Newer agents have a safer side-effect profile but are not risk-free; TD still emerges in approximately 5% of treated older patients each year, in keeping with the young to old risk ratio of 1:5 observed with first-generation medications (Correll et al., 2004). Older people are also more sensitive to EPS, even with second-generation antipsychotics like risperidone, and this risk may be higher for those with EOS (Jeste et al., 1995; Lemmens et al., 1999). Other related side effects include orthostatic hypotension, cardiac conduction abnormalities, agranulocytosis, and neuroleptic malignant syndrome (NMS). Hyperprolactinaemia from dopamine blockade is associated with osteoporosis, increasing the risk of hip fractures (Boyce, 2008; Reeves and Brister, 2008; Sachdev and Brodaty, 1999a). Both classes of antipsychotics have been implicated in increasing cardiovascular and all-cause mortality (Isaac and Koch, 2010; Kales et al.,

2007; Kelly et al., 2010; Schneider et al., 2005). Age-related changes in liver and kidney function, decreased lean body mass, and polypharmacy may additionally impact the pharmacokinetics and pharmacodynamics of antipsychotics (Sable and Jeste, 2002; Tsuboi et al., 2011).

The International Consensus suggested that one-half to one-quarter the doses of that used in younger patients could be used in LOS patients and as low as one-tenth in VLOSLP. The initiation of therapy should be made at a very low dosage, with cautious increments up to the lowest effective dose (Howard et al., 2000). For example, risperidone should be introduced at 0.25–0.50 mg/day and titrated by no more than 0.50 mg/day to a target range of 1.25–3.50 mg/day. Starting and target dose-ranges of olanzapine should be 1–2.5 mg/day titrated up to 5–15 mg/day. With quetiapine these should be 12.5–25 mg/day titrated to 100–300 mg/day (Alexopoulos et al., 2004; Jeste et al., 1996; Reeves and Brister, 2008). Recent data suggest the efficacy of aripiprazole with doses as high as 15–30 mg/day, but some recommend the more modest target of 10–15 mg/day, introduced at 2 mg/day (Coley et al., 2009; Kohen et al., 2010; Madhusoodanan et al., 2004; Rado and Janicak, 2010). Lower dosing strategies have been suggested for late-life psychosis in the context of delusional disorder or dementia (Tsuboi et al., 2011). Amisulpride has also been demonstrated to be comparable to risperidone in older patients and doses of 200–400 mg/day have been used, introduced at 50 or 100 mg/day (Psarros et al., 2009). More recently, the ATLAS trial (Howard et al., 2018) reported that a daily dose of 100 mg of amisulpride was effective and well tolerated. Depot medications may have a more continuous delivery and are often used in nonadherent patients, minimizing the plasma level fluctuations that can be especially problematic in older people (Lasser et al., 2004). Long-acting risperidone at doses starting at 25 mg every two weeks was shown to be safe in older patients followed for one year. Some patients received and tolerated doses as high as 75 mg every two weeks (Kissling et al., 2007; Lasser et al., 2004; Singh and O'Connor, 2009). As in the younger population, depot formulations have not been found to be more effective than oral antipsychotics if adherence is good (Reeves et al., 2002). Paliperidone extended-release (ER) consists of the active metabolite 9-hydroxyrisperidone in a tablet using patented extended-release technology to provide continual and consistent delivery over 24 hours. It has theoretical advantages in older people, like a once-daily schedule, minimal hepatic metabolism, potentially fewer side effects, and limited plasma fluctuations in cases of missed doses (Turkoz et al., 2011). In a 30-week trial involving patients around age 70 with EOS and LOS, paliperidone ER was found to be safe and well tolerated, with an age-related increase in somnolence and tachycardia. Age of onset did not impact these findings. Paliperidone also seemed to be effective at reducing symptoms, but the study was not powered to assess this outcome. Dose range was 3–12 mg/day and started at 6 mg/day (Tzimos et al., 2008).

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According to a survey of expert clinicians in the US, risperidone should be the drug of choice in late-life schizophrenia, and quetiapine, olanzapine, and aripiprazole are good second-line options (Alexopoulos et al., 2004). There is more limited evidence regarding the use of ziprasidone and clozapine and none for LOS specifically. Clozapine especially should be used with caution considering its side-effect profile and important anticholinergic activity, and polypharmacy using more than one antipsychotic should be avoided.

Adjunctive medications

Although younger age is correlated with a more frequent use of adjunctive mood stabilizers for schizophrenia, recent data support their use in older people as well. Adjunct ER valproate (mean dose 587.50 mg/day) was effective and well tolerated in an open-label study on 20 older chronically ill patients, and was associated with symptomatic improvement, better global function, and lower depression scores (Sajatovic et al., 2008; Sim et al., 2011). The resolution of comorbid depressive symptoms with adjunctive phytoestrogens in a woman with LOS was discussed in a case report (Rakesh et al., 2011). Cholinergic neurotransmission has been implicated in psychosis and visual hallucinations, but there is currently no evidence regarding the use of cholinesterase inhibitors for this purpose, although there seem to be a role for them in management of associated cognitive deficits (Patel et al., 2010; Ribeiz et al., 2010). There is also a theoretical rationale for the use of memantine and reports of a positive impact in cases of catatonic schizophrenia (Zdanys and Tampi, 2008). To our knowledge, there are no data supporting the addition of these agents in older adults, particularly those with LOS.

Addition of SSRIs, specifically citalopram, has been shown to be effective in treating subsyndromal depressive symptoms in older persons with schizophrenia. More importantly, such treatment may reduce risk of suicide.

There is supporting evidence regarding electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) for refractory symptoms in younger patients with schizophrenia (Matheson et al., 2010). To date, there are no publications reporting LOS treatment with ECT, but rTMS in LOS has been the focus of a case report, describing one individual with auditory hallucinations successfully treated with both acute and maintenance rTMS (Poulet et al., 2008).

A few recent studies have suggested efficacy of oestrogen therapies for schizophrenia, although the overall evidence is weak. Several open label and randomized controlled trials of estradiol derivatives and conjugated oestrogen in premenopausal women have demonstrated improvements in positive symptoms (Akhondzadeh et al., 2003; Ghafari et al., 2013; Kulkarni et al., 1996; Kulkarni et al., 2015; Kulkarni et al., 2001, 2002) and cognition (Ko et al., 2006). However, two studies did not report any

significant symptom improvement with oestrogen treatments—one using a combined estradiol-progestin therapy and the other studying a conjugated oestrogen therapy (Bergemann et al., 2005; Louza et al., 2004). Two studies of raloxifene, a selective oestrogen receptor modulator (SERM), have reported improvements in cognition (Weickert and Weickert, 2017) and brain activation (Ji et al., 2016; Kindler et al., 2015) in premenopausal women. The raloxifene studies in postmenopausal women generally include only EOS patients and have shown some improvements in positive and negative symptoms (Kianimehr et al., 2014; Kulkarni et al., 2010; Usall et al., 2011; Usall et al., 2016). In men, one study showed that two-week estradiol treatment rapidly improved psychopathological symptoms (Kulkarni et al., 2011) and that eight-week raloxifene treatment led to greater improvements in negative symptoms and general psychopathology (Khodaie-Ardakani et al., 2015). One case report described improvement in psychotic symptoms with hormone replacement therapy alone in a perimenopausal woman with LOS (Bergemann et al., 2007). Notably, the largest published study of raloxifene plus antipsychotics versus placebo plus antipsychotics in 200 severely ill decompensated postmenopausal women with schizophrenia or schizoaffective disorder was a 16-week double-blind randomized controlled trial. It reported that individuals in the active treatment arm had *worse* outcome than those in the placebo arm. The authors concluded that their data do not support the use of raloxifene in severely decompensated patients with schizophrenia or schizoaffective disorder.

To date, no published trials have examined the therapeutic use of oestrogens or SERMs in LOS patients of either gender.

A recent open-label trial of yokukansan, an herbal remedy with serotonergic, dopaminergic and glutamatergic actions that has been studied in treatment-resistant schizophrenia and dementia patients with agitation (Matsuda et al., 2013), found significant improvement in psychotic symptoms in patients with VLOSLP compared to placebo (Miyaoka et al., 2013).

Valbenazine, a selective vesicular monoamine transporter 2 (VMAT2) inhibitor was approved by the FDA in April 2017 as the first and only approved treatment for tardive dyskinesia in adults. Unlike tetrabenazine, a VMAT2 inhibitor that is approved for Huntington's chorea, valbenazine is dosed once daily and had few side effects related to monoamine depletion (Huntington Study, 2006). The once-daily dosed medication was shown to significantly improve movement systems as rated by the Abnormal Involuntary Movement Scale and Clinical Global Impression of Change—Tardive Dyskinesia over a six-week trial and was well-tolerated in the participants (Hauser et al., 2017; O'Brien et al., 2015). These trials were conducted in patients aged 18–85 years old, with average age 55 to 57 years. More than half of the participants were diagnosed with schizophrenia or schizoaffective disorder, though a number of participants with mood disorders and gastrointestinal disorders were also included. It is unclear what proportion of these participants had LOS

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compared to EOS. Further studies on the effects of this new tardive dyskinesia treatment in LOS are warranted to finetune its use in older persons.

Psychosocial treatments

Most trials of psychosocial interventions for older persons with schizophrenia have targeted patients with EOS. Keeping in mind the significant differences in premorbid psychosocial functioning between those with EOS and those with LOS, there is a need for studies comparing results of psychosocial interventions in early- and late-onset patients. Psychosocial interventions can have significant benefits other than immediate symptomatic relief. For example, a socially stimulating group intervention targeting lonely older individuals with schizophrenia has been associated with better cognitive functioning, improvements in wellbeing, and lower mortality (Pitkala et al., 2011; Routasalo, 2009). This is particularly relevant to the LOS population impacted by high prevalence of social isolation, which has also been found to increase the risk of dementia (Wilson et al., 2007). Three nonpharmacological treatments have been designed specifically for the older population with schizophrenia and they are all group based.

Functional Adaptation Skills Training (FAST) and its modified version for older Latinos—Programa de Entrenamiento de Aptitudes para Latinos (PEDAL)—are manualized therapies implemented in the group format. Both have been found to improve social and everyday functional skills and to decrease the short-term use of emergency medical services (Mausbach et al., 2008; Patterson et al., 2006; Patterson et al., 2003).

Cognitive-behavioural social skills training (CBSST) is another group intervention designed for older people with schizophrenia. It combines two modalities with efficacy in younger patients. CBSST is based on the concept of challenging the common beliefs that interfere with treatment in this population and by providing repetitive practice of behaviours to improve retention and skill development. It has been associated with learning of new coping skills and better social functioning after treatment and also at one-year follow-up. However, gains in cognitive insight following CBSST appear to not be maintained at follow-up. This suggests that improvements in function are not necessarily an outcome of better insight (Granholt et al., 2005; Granholt et al., 2007; McQuaid et al., 2000).

Enhanced skills training (ST) and healthcare management (HM) combine skills training for daily living and medication management plus preventive nursing visits to address medical comorbidities in older adults with severe mental illnesses (SMI). ST + HM has been associated with improved social functioning and independent living skills, whereas functioning remained constant or declined for the HM-only group. The two groups receiving HM demonstrated increased use of preventive health services and identification of previously undetected medical

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disorders (Bartels et al., 2004). A derivative, Helping Older People Experience Success (HOPES), is an integrated model of psychosocial rehabilitation and healthcare management and appears helpful in improving community living skills (Pratt et al., 2008).

The potential benefits of employment are numerous and older adults with SMI often manifest a desire to work despite low rates of paid jobs (Auslander and Jeste, 2002; Twamley et al., 2005). Ageing with schizophrenia can be associated with challenges in the workplace (Jeste and Nasrallah, 2003; Kurtz, 2005). However, competitive employment and, specifically, supported employment (SE) has been associated with better outcomes compared to conventional vocational rehabilitation (CVR). The goal of SE is rapid and individualized placement in competitive work with on-site training if required, following the 'place-then-train' philosophy. CVR reflects the 'train-then-place' approach with prevocational training and volunteering and gradual contact with competitive work (Twamley et al., 2005; Twamley et al., 2008).

Treatment adherence and service utilization

No study has assessed treatment adherence in patients with LOS specifically, but both psychosis and ageing have been linked to adherence problems. Partial adherence to treatment is observed in at least 20–50% of patients in the general population, but these rates approach 70–80% in persons with psychotic disorders. In older patients taking antipsychotics and medications for hypertension, diabetes, or hyperlipidaemia, researchers have reported similar adherence for psychiatric and nonpsychiatric medications. These rates ranged from 52–64%. Several factors related to old age may result in poor adherence, including sensory impairments, cognitive deficits, osteoarthritis, restricted mobility, lack of transportation, social isolation, financial insecurity, polypharmacy, and increased sensitivity to side effects. Poor adherence is associated with recurrence of symptoms and readmission, and with significant personal and societal costs (Masand and Gupta, 2003).

Studies have shown that among the population with chronic psychotic disorders, older age is associated with a lower use of all mental health services, with the exception of case management. This is in keeping with the observed decline in mental health expenditures in older people and the fact that the higher costs of case management and inpatient/crisis residential services among older persons are attributed largely to the population with schizophrenia. A significant drop in the use of outpatient services has been noted with age; this might explain the more frequent use of psychiatric emergency response teams and psychiatric emergency unit admissions (Gilmer et al., 2006; Jin et al., 2003).

These findings are consistent with those of McNulty and colleagues (2003) describing the high level of unmet care needs in a community sample of older people with schizophrenia or related disorders in Scotland, 59% of them with onset of symptoms after age 45. Reeves and

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colleagues (2002) also observed that only 59% of older people previously diagnosed with VLOSLP were still in contact with psychiatric services after three years. A 2016 UK study reported low antipsychotic treatment rates (48% at three months, 27% at 12 months) in patients with VLOSLP (Sin Fai Lam et al., 2016).

It is also critical to assess capacity for healthcare and financial decisions. There is considerable heterogeneity in the level of decisional capacity among patients with schizophrenia, and age itself has not been found to strongly predict the lack of capacity to consent. Negative and cognitive symptoms have a more significant impact on the decision-making capacity than psychosis per se, and capacity should be assessed when appropriate, by using instruments such as the MacArthur Competence Assessment Tool for Treatment (MacCAT-T) (Grisso et al., 1997). Advanced care directives should be reviewed in any patient, but even more so in older adults, and should minimally include a discussion on living will and proxy decision-making.

Prognosis

Course of symptoms and functioning

Considerable reductions in schizophrenia symptoms have been observed in persons with LOS treated with antipsychotics. Open studies of typical antipsychotics have reported full remission in 48–61% of patients and higher proportions of at least partial response (Howard et al., 2000; Sable and Jeste, 2002). Better results have been noted with second-generation antipsychotics, even in the VLOSLP population, with substantial improvements noted in up to 77% of patients, with a more favourable response in those from outpatient vs inpatient settings. In older people treated with atypical neuroleptics, a more positive outcome could be seen in those with LOS as opposed to EOS (Barak et al., 2002; Scott et al., 2010).

Mazeh and colleagues (2005) followed 21 inpatients fulfilling criteria for schizophrenia with first onset at age 70 or later for a mean duration of 30 months. They compared this group to 21 older inpatients with onset of schizophrenia before age 40. Worsening of symptoms was reported in only one VLOSLP subject. Most had a single episode with full or partial remission, while almost one-half of the EOS patients experienced a relapse. The choice of the control group might have biased the findings, as the literature suggests that ageing is associated with an overall improvement in psychosocial function and psychopathology in older adults with EOS, although most remain impaired (Auslander and Jeste, 2004; Jeste and Nasrallah, 2003; Jeste et al., 2011). The findings in LOS patients are in keeping with results for the VLOSLP population reported by Reeves and colleagues (2002), with 52% having a single admission. Similarly, Brodaty and colleagues (2003) followed individuals with first onset of schizophrenia at 50 years or older, and observed a considerable decrease in symptomatology over time; 68.4% of them fulfilled DSM-IV

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criteria one year after the diagnosis, and only 16.7% met criteria at five-year follow-up.

However, the broader literature tends to suggest partial, rather than complete, symptomatic improvement over time in LOS and VLOSLP, which mirrors the literature on late paraphrenia from the 1960s (Kay and Roth, 1961). Jeste and colleagues (1995) reported that most of the LOS patients in their sample had a chronic course with illness duration longer than two years, with an average of 5.7 years $SD \pm 5.5$. Copeland and colleagues (1998) described residual symptoms and no case with complete recovery in subjects who had developed schizophrenia after age 65, although worsening was not seen either. Meesters and colleagues (2011) observed no significant difference in rates of symptomatic remission among those patients with early, late, or very late onset. Literature on psychotic disorders in late life seems to indicate that female gender, good treatment adherence, and schizoaffective illness are predictors of a favourable outcome. Findings are more inconsistent regarding the impact of cognition, sensory deficits, and ethnicity on the course of illness and psychotic symptoms specifically, although cognitive impairment has been associated with worse functional status (Auslander and Jeste, 2004; Granholm et al., 2008; Harvey, 2001; Palmer et al., 2002). People diagnosed with LOS and delusional disorder do not seem to differ in terms of outcomes. A dose-related effect was shown regarding antipsychotic use. Contact with a community psychiatric nurse also appears to lead to a more favourable course in LOS and late paraphrenia (Hassett, 2002; Holden, 1987; Howard and Levy, 1992; Meesters et al., 2011; Reeves et al., 2002; Riecher-Rössler et al., 2003).

Partial improvement in symptomatology can be achieved in most patients, though this does not necessarily translate into functional recovery (Patterson et al., 2003). Brodaty and colleagues (2003) demonstrated that even though the majority of LOS patients did not meet DSM-IV criteria for schizophrenia at follow-up, they were still functionally impaired, with GAF scores still below 50. Nineteen of the 21 patients included in a follow-up study by Mazeh and colleagues (2005) were able to stay at home for 30 months following discharge. Mild difficulties in the activities of daily living (ADLs), still within the normal range, characterized the 13 subjects with LOS described by Laks and colleagues (2006), with no significant deterioration in the functional scores at the one-year reassessment. These results underscore the heterogeneity in clinical and functional outcomes in the LOS and VLOSLP populations.

Course of cognition

Although there is no indication of an increased risk of Alzheimer's disease in patients with LOS, some data support a general neurodegenerative pathophysiology. In follow-up studies on LOS or psychosis, significant cognitive deficits have been described in up to 50% of patients, especially

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in very-late-onset cases (Brodaty et al., 2003; Korner et al., 2008; Korner et al., 2009a, 2009b).

Yet, most of the evidence points towards relative stability in the cognitive abilities of patients with LOS. Palmer and colleagues (2003) found no evidence of cognitive decline for schizophrenia patients in both late- and early-onset groups compared to normal controls, while two Alzheimer's disease comparison groups (persons with very mild deficits and persons with psychotic symptoms at baseline) manifested progressive impairments. The absence of significant change in neuropsychological performance over time in individuals with LOS has been replicated. Although people with LOS do not experience a greater worsening of their cognition compared to age-matched controls, they do not show the same level of improvement following intervention (Granholtm et al., 2010). This could have treatment implications, as it suggests a ceiling effect in response to interventions that have a cognitive remediation component.

Quality of life

In older patients with schizophrenia, symptomatic remission has been associated with a higher reported quality of life (QoL), intermediate between that of younger patients and healthy comparison subjects (Auslander and Jeste, 2004; Bankole et al., 2008). A study by Folsom and colleagues (2009) suggested that older age may, in fact, be associated with greater mental health-related QoL in this population. On the other hand, Meesters and colleagues (2011) could not demonstrate any correlation between symptomatic remission and QoL in older people with schizophrenia, although the remission rates in their sample were lower than those reported from convenience samples. This is consistent with studies indicating significantly greater improvement in psychological and health-related QoL in patients treated with olanzapine rather than risperidone (Ritchie et al., 2003; Ritchie et al., 2006). In light of the significant interplay between cognitive status and social situation with regard to overall function and QoL, the failure to include measures of QoL in most outcome studies on LOS or VLOSLP as well as the exclusion of late-onset patients from some papers on QoL area is a drawback (Meesters et al., 2010).

A similar effect to medications has not been as clearly established with psychosocial interventions. No impact on QoL was demonstrated following participation in FAST (Patterson et al., 2006; Patterson et al., 2003). Improvement in QoL resulting from better functioning following CBSST was postulated by the authors, but as QoL was not part of the outcomes measured, this remains hypothetical (Emmerson et al., 2009). We did not find any mention of QoL in relation to ST + HM (Bartels et al., 2004). However, vocational rehabilitation, particularly supported employment, does appear to lead to better QoL (Bartels and Pratt, 2009; Twamley et al., 2005; Twamley et al., 2008). This could indicate that better functioning seems to be associated with greater wellbeing; other avenues also need to be considered. The importance of positive social

support and interactions cannot be minimized, as married middle-aged and older adults with schizophrenia reported better QoL, despite the presence of depressive symptoms in both groups (Nyer et al., 2010).

Mortality

While increased morbidity and mortality rates have been noted in schizophrenia for decades, recent studies have reported a growing mortality gap between individuals with schizophrenia and the general population (Laursen and Nordentoft, 2011; Lee et al., 2017; Saha et al., 2007). Whether late-onset cases herald a specifically higher mortality risk is not clear. Most outcome studies reporting deceased subjects did not include a control group. The onset of psychotic symptoms in late life was associated with double the risk of mortality at follow-up by Henderson and Kay (1997), while Östling and colleagues (2007) found no such association. A 2015 Finnish registry study reported that VLOSLP had higher mortality risk compared to EOS patients, mostly attributable to physical comorbidities and accidents (Talaslahti et al., 2015). Although the risk of suicide might be somewhat lower in older patients with schizophrenia by approximately 5% compared to younger affected individuals, they are still at risk of suicidal behaviours, and age of onset was not found to mitigate this risk one way or another (Barak, 2004).

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Personal experience: The red and the reason

Chapter: Personal experience: The red and the reason

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in my garden,

red rose,

redbreast,

the raw and its roots - the red and the reason¹

It takes me years to find my garden, sixty-eight to be precise, although there are other gardens of one sort or another before this. Sitting here among the leaf-stripped trees with this sense of fullness and completion, of tranquillity and something akin to contentment though neither joy nor absence of pain describe it fully, sitting here, I watch the robin tremble a bare bough and see the strangled rose shed its crimson to the wind.

Personal experience: The red and the reason

Beginnings

I come from a line of women living traumatic lives. My great-grandmother survives emigration from Ireland and the death of a husband who does not. She self-medicates with alcohol and forgets she is a mother. Her two daughters are farmed out to a family where they are exploited as cheap labour and where unspeakable acts take place. Mama guards her sister with fierce love, and nurses a violent hate towards the abusers. My grandmother goes on to birth two children of her own and to build her life around them. And when my mother is deserted by my father, she comes back home to the love of Mama, with me her daughter in her arms. I grow up in this way, fatherless, but with two mothers, inside of a citadel where men are enemies.

I grow up in a maelstrom of love, loss, and pain, snatched up into a fierceness that twists control from my mother, crushing her into submission as daughter within the fortress that Mama rules. But in this stronghold of love, built to protect us from the world and its wounds, the cruellest wars are waged within. Domestic conflicts between mothers and daughters.

Women at war with one another. Women at war and women in peace, flash truces marked each evening with the wine opened and the beer poured and pain laid temporarily aside. There is laughter, warmth, comforting. Mothers sit down, work done, quarrels mended, the Guinness and the Keystone Port drunk in libation to the mantra that 'iron is good for you.' Mama is anaemic from childhood. Migraine crushes my mother. The heart breaks, the body bears the ills, the bottle brings relief ...

I witness the violence of women on women. These raw memories are not softened by time. Hard words and screams pierce the struggle for charge of the child, where home-front shifts to battleground. Household tasks become war crimes, with sweeping brushes hurled, as tempers bristle and rage rends itself into cleaning frenzy, then the silence so taut it threatens to shatter the windows polished to a thin edge.

I smell the wounds of mother love turned against itself. I taste the gall of married love abandoned. I watch despair lashed out with stinging threats and accusations ...

I am a witness to violence and I am subject to it. My mother's sharp words linger longer than the slaps across the face. And now, in later life, I find myself both war correspondent and war casualty, and surely war criminal also.

Yet my heart's wholeness is comfort to me as I age. It reminds me that, regardless of pain, I am as a child most deeply loved, through many sacrifices and deprivations, on the part of two women to protect me. And I feel such a tenderness for our broken lives, where we try our best and

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do not succeed. I carry the love, the loss, and the longing and I hold no regret. For these are the memories that please and sadden together.

I savour rain steeped in the damp wool of my mother's coat from her long walk to night class, before she sits through the night to sew me a dress. I inhale bleach from Mama's apron as I watch her work while I play and then I feel the grasp of her hand walking me to swim after school and the same chlorine smell from the baths when she towels away at my shivering, before we wait the trolleybus home in the dark night. I sniff the scent of cakes from the oven that could hardly wait to cool before we tear into them and I feel all the love of their baking.

I can never, never as a child remember feeling hungry without the prospect of food to take that hunger away. I can never recall the humiliation of torn clothes as my mother parades me, her velvet princess, around the marketplace, without a penny in her pocket.

Within reminiscences such as these lies the comfort of childhood, but also the remorse that comes with insight; of a generosity taken for granted, of privilege earned through the going without of others, and those many opportunities outside the limits of our family income that come to me not by chance but through maternal determination and belief in a better future.

The good memories far outweigh harder ones in their lasting impact on my survival and spiritual growth. I am able to look on my life as anchored by strong maternal love that, in turn, has enabled a core of resilience, of eventual self-belief, and some sort of wholeness. And I carry a depth of love in return for both of these mothers who have nurtured me.

It is impossible however to negate the traumatic effects of early experiences and the wounds that left untreated have cankered into my body, mind, and soul. In recalling pain as a witness, the actions of the women who love me most must be called to account.

Yet as I flay back time to lay bare the past, I suffer the guilt of family love betrayed. For many years, I choose not to make the inner journey. It feels treacherous to unpick sacrifice and it is only now, in my sixties, that I feel the need to know myself better and understand where my life has led me and why. So let me say, that 'war-crimes' have been absolved long, long ago. What needs to be let go of, forgiven, and forgotten, the pain pushed down and plunged into the recesses of my past. It is only now that I come to confront the red and the reason.

In resurfacing, it is the trauma of generations that tells itself, hurt passed down from mother to daughter, suffering and surviving, familiar in shape and shadow, inevitable in its outcomes.

I trace scars and feel a sadness seeping out from the warp and weft of my mother's coat. Pain worn in silence, its weight stumbling and suffocating, eyes shut against tears spilling. Sssshhh! Sssshhh!

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Sorrow in her voice as she begs the man in the bare room to give her, please, a cup of tea.

How I do recall this visit to my father, where I am still a babe in arms? my mother wonders, when we share the story as adults! Yet I hear the pain of hope lost as if it were yesterday. The shards of broken wedding vows and grief unassuaged in its strongbox imprint upon me the need to lock up my emotions. Strong women have no need for tears. Suffer on in silence. I am denied permission to cry from an early age. Fear however needs no one's permission.

Fear sucked in from the breast and trembling in every fibre of flesh, thought, and feeling.

Fear for the absent father and a carving knife in Mama's hands ever waiting him at the door. Fear of the kindergarten scorn towards a girl without her daddy. Fear when the pretty poppy crumples in my five-year old hand and I dare not own to breaking it. Fear of folk on our street who must never be spoken with because Mama says they are not like us. Fear so crippling I become paralysed at the very thought of other people and I build an inner world as refuge.

Aged nine then, blood on my mother's undergarments and I fear for months till I learn she is not dying. Till I come to discover the meaning of womanhood. Terrified, when my own time arrives, I bury its evidence in the garden. In a house of secrets, I do not allow myself to bleed.

I do not allow myself to bleed unless I control it. I dig down deep to bury the disgrace and I smell the dank earth on my soul. The garden is my hiding place. I guard it anxiously.

In the house of secrets, there are no maps for the body changing from child to woman. Mothers do not share with the daughter-child-woman, the legacies of desire and adult love. Only allowed to know that men are dangerous, unwelcome. Women guard their daughters and deny them knowledge of the flesh.

And at the age of eleven I begin to cut chunks out of my own skin in a rage at my body.

the garden of guilt,
red handed criminal,
red faced disgrace,
the raw and its roots - the red and the reason

And rage suppressed reveals itself in splashes of red.

Red roses on the wallpaper in the room I share with my mother. She is a beauty in her white tight shift with the red roses that she wears, to pierce hearts of the men she traps in triumph. Males keep out! scream the roses

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on the walls. You can look but do not touch, snigger the roses on the dress. Come close and we will draw the blood from your eyes.

Night study brings advancement for my mother. Always a worker, breadwinner by necessity, now an achiever, she flies high from typist to teacher, from teacher to author to expert; ruler in her own domain. She is a queen. Men kneel before her knowledge and they are enslaved. She captures them with her beauty. The queen of roses collects hearts to lock away in her strongbox. She is loved but loves not. Blood for blood, to appease the broken bride.

Violence breeds violence. It leads me to seek out the red in my adult life. The crimson that blossoms early is slashing out the path I will follow. Its seeds planted within the small child.

I ripen to a teenager in the face of the mother queen. Her secret lusts and longings stare her straight back in the eye and mock her. My awakening is a gauntlet thrown to challenge what she most denies. The queen lashes out in a raw red rage and I harvest the yield of her envy.

I feel the fire of the red on my face. I smother the urge to strike back. I rip up photographs, scoring out their smiles. But the images I destroy are never my mother. I tear only at myself.

I feel the power of anger, am paralyzed when there is no place to put it, Rage turns inwards.

The knowledge that I hurt myself more deeply than others can, is exhilarating and addictive.

My mother runs to London. She is called to high places. I am left with Mama and I run wild.

I hurt myself to hurt the mother who cares for her career and who runs away from my pain.

I cry unheard for help, I ask for answers from women who shut their ears to the questions.

So I am drawn to the power of men, one after the other they pursue me, and I hate them all.

The grandmother spoils the pretty grandchild, more kind than she was to her own daughter.

I fritter away new freedoms, find bad company day and night, lose all sense of direction.

I become a precarious woman amongst precarious women in the house of sorrows unshed.

Weekends bring us together. At my most provocative, I flaunt insolent flesh out of spite.

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The queen screams at bared breasts, rails at white thighs, hates the hippy hair in armpits.

The slapping continues until I am twenty and I hit back. My mother never strikes me again.

I meet my man at twenty-one. I move to live with him and the family cease speaking to me. In hospital, I recall the mothers sitting tight lipped and wordless until I am out of danger and they can leave.

I marry my husband within the first year. After one wedded week he punches me in the face. He takes me into the garden and pushes me towards the canal. This is where wives end up. I do not run home to the mothers. Shame bolts me to the marriage bed where I must learn that his violence is all my fault. I've made my bed and I must lie in it, since I chose to leave the mother house; the house that denies all men.

It takes me four years to shake off the shackles of blame and leave him. It takes forty years before I can write about it. It takes forever to become free ...

I survive alone. I am proud of this. I make it through homelessness in the seventies, before the birth of the refuge and the safety of Women's Aid,

And my bed must be any bed. Bed is a child's bunk in a friend's home, bed is the temporary sofa where my presence does not push the unquestioning kindness of work-mates, bed after nights of painting red, is any crash-down with anyone at all. I take any bed because I do not have a bed of my own.

I am proud that I do not splinter. Strong women bear their burdens. I learned the lessons at my mother's knee. And so I push down the pain until my physical body screams in protest. At the age of twenty-six I am asthmatic, arthritic, with a heartbeat that flutters and threatens.

It will take a decade before I break into pieces, ten years until I make the link between the ills of body, mind, and soul. I will dig the roots of distress to shake loose the red and the reason, before I become whole again.

Breaking down and building up

in the garden of pleasure
is the red dress to dance in
Is red wine in the morning
the raw and its roots -
the red and the reason

My late twenties and thirties are a whirl of new experiences and it comes my time to fly high. I land back each Friday to the mothers where I am now on safer ground, where theirs is a house of food and wine and the cosy chatter of women pecking on the scraps of the week. My mother is my role model. Women are achievers. Strong women can do it for

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themselves. I pick up an education. I pick up a career. I pick up a house. I throw off a violent marriage. I am working in a university. I have lodgers to feed the mortgage and I feed them each night. My own home becomes my castle. I fill it with the folk who know how to enjoy.

And I too become a queen. I am the queen of parties and good times. We dance in the garden and we dance down the street. My house is full of the good timers from dusk till dawn and I go from empty to empty with a hunger that I cannot name and do not even taste.

I do not know I am starving. I do not want to think about the deeper hunger, so I do not think. There is always the next thrill to push the pain down, another love to consume the craving.

I am thirty-six when I start to cry and I cry for most of my lifetime in the space of a weekend. The time and the place are irrelevant. It is only important that the tears begin and that once they are pouring down my face, there is no way to quench them.

I sit among my people and I have never felt so lonely. Nothing matters any more but the tears and the clarity that they bring. I cry until the emptiness inside me is flushed out and hung up to dry. I look on with peeled eyes and I weep in despair at what I see ...

I have never felt so lonely and yet I know that I have been this lonely for the whole of my life.

I must howl to the moon. I must dance close up with pain. I must lie in the empty bed, abandoning the lover who gives me his back. I must not be afraid—and if I am afraid I must understand and I must forgive myself.

It is the breaking down that saves me. In the hard months ahead I find the roots of fear and loss and rage. I learn to be alone and to be at peace with myself, to hold the broken bits and not be ashamed. I learn that fear of fear is maybe the greatest fear of all. I trace my body's ills to their spiritual sources and begin to integrate my body mind and soul. I will, I can, heal.

And I build up a better self. I find reason and love, in work, in life, in a reaching out to others. My links to the mothers are stable and calm but I share not my breaking. From this pain will I guard them and I will spare them. I will carry my own broken back as they have taught me well to do. For in their love, they do the best they can, the mothers in their sorrows.

my mother's garden
red shawl on an empty seat
red eyes weeping
the raw and its roots -
the red and the reason

Personal experience: The red and the reason

In my grandmother's ageing, my mother finds a new power. The homestead is hers to rule and her caring becomes the silken ties that hold down Mama within the citadel of kindness. Trapped in blindness as great-grandmother before her, an agile angry mind in a dark prison the final years bring comfort to my grandmother at the price of her independence. Mother is now the giver of food and the maker of rules, coaxing the broth before the brandy, bleaching the unsightly hairs from Mama's chin and scolding the soiling of the bed.

Mama dies at home in the care of daughters. She asks me and I tell her that she is dying. She is so peaceful to know that life will close, for ageing has neither been welcome nor kind. I carry my Mama on my back to the bathroom. We laugh at life with all of its indignities. Her pain is brief and in the final hours, she sees faces that we cannot see. She sees forms that she knows and she speaks with them.

I am happy when spirits visit and lift the veils from her eyes. I feel the freedom of her passing and my tears at her end are tears of joy. My mother feels nothing but loss, inconsolable loss and the gaping hole left after the years of caring. When after weeks, she can weep no more, her skin weeps for her and she succumbs to wretched afflictions of skin and the soul.

Rage not laid to rest, festers raw under the surface, trapped in the grief that won't let go.

My mother ages quickly. She feels emptiness that is not relieved in the company of others. She wants the closeness in the house of mothers where she now lives alone. She is angry when I bring her disappointment for I will not be governed by what has gone before, by rage disguised as duty and in petty little paybacks wrapped up and hidden within the kindness of unstinting daughter love.

We travel on together, my mother and I, sometimes at peace, sometimes at war, meeting by arrangement, always at mercy to the angry flare-ups that set us alight against one another. She longs to nurture and feed. She tears at food with her fingers to put on my plate. She waits by the phone. She plans in smallest detail her life around mine. She will help my work. She will find us evenings of music and theatre. Mother and daughter enjoying themselves.

'She should have died hereafter'—my asthma smothers Macbeth and shakes his soliloquy. I struggle against the silent audience for I must leave my seat, my mother stumbling, clinging on. I gasp and my mother weeps. My mother prays and I gasp. I gasp at her to leave me be. Bereft of breath, I am without care and without kindness. I cannot and I will not hold her pain.

A lifetime of breath suppressed, in the minutes before I can express and I say her concern is concern for herself—she does not see how she makes me worse—that I cannot find air while she panics—that I cannot save her

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and myself at the same time—I fight her for the space to breathe. She says in fury that I push at her when she tries to help. She is angry at being rejected in a time when I need her least.

It is weeks before we forgive one another.

Age will mellow; me in my fifties she in her seventies, we will dig out time for the unspoken.

My mother asks why I am distant and never the dutiful daughter as she herself has been.

'... because you were never there for me ...'

I answer from some untapped pain-source within. I feel in its intensity the stab of unbearable abandonment of the child whose mother puts a career first.

Releasing her own pain, my mother replies:

'... I had to run away because Mama wanted you all for herself ...

... I could never be the mother I always wanted to be ...

... I had to run away to find myself and make a different life for us all ...'

agony in the garden
red alert
red pain at work
the raw and its roots
the red and the reason

I spend more time with her as she ages. We slip into an understanding and an acceptance of one another that honours what has gone before and gives to the moment what is needed.

My mother's death is not easy. Illness comes and kills quickly and without any warning. Her pain grows until she can bear it no longer and an ambulance is sent for. Doctors find the spiteful cancer hiding itself out of sight deep within her. Hours from death, and I would change places to spare her these hours. In a pen packed with older people, she is examined by a doctor, who ignores her cries and forces a feeding tube inside her. The terrified animal in her eyes leaps trembling into my heart and remains there to this very day.

My mother, wheeled unconscious to ICU, where they tell me it is just a matter of time.

I sit at her side and I talk, I talk and I sing. I do not leave her alone in the darkness without the sound of my voice for one moment. Our lovely Father Sean is there, too. In a brief silence as I gather my feelings, my

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mother's eyelids strain to open and she searches for my voice. I tell her that I love her and that I have always loved her and that she is the most beautiful person in the whole world and all of this I say from a true heart. I sit holding her hand for seven hours, though the nurses try and fail to move me.

The nurse tells me that my mother's breath has stopped. The nurse wraps her arms around and hugs me. I have no tears and no pain, nothing but exhaustion.

I must find my mother her prettiest dress, I will drape her coffin all over with sweet red roses. Two hundred red roses say goodnight and god bless to the mother sleeping in the church.

I am the daughter bereaved, not of one mother, but of two. I am the end of history. This tale of mothers and daughters will end with me. No daughters to follow my wake. I travel alone, stripped of status, bereft of their company, the mothers who leave me behind.

the garden smoulders
red flames in the night sky
red flag, mind missing
the raw and its roots -
the red and the reason

My own beloved home is burgled and razed to the ground. Coupled with my mother's death. The mind breaks and I am made mad. Spiritually gutted, burned to ashes; nothing, nothing. I am a refugee from myself. I am refugee and I am orphan. Besieged with fears and regrets, pursued by guilt, all meaning is lost.

I am a wanderer. I am without possessions. All that matters reduced to rubble. A lifetime's work and writings gone up in smoke, beloved books burned to ashes, pictures of mothers consumed by the flames, love charred at the edges within smouldering memories.

But madness is not unkind. I find solace within the visions that hold me. Red tempers reason and I rise from its flames durable, resilient renewed with a core of steel. All that is unwanted is seared away. I have been broken and I have fused myself together.

This is not easy. I am still at mercy to ghosts. But I am learning to live with fear and face it, and to answer the spectres of the past as truthfully as I can. I am integrated into something whole that I can call my ... self.

I am strong woman and I am naked woman, terrified and courageous, fractured and whole. And I am the legacy of my two mothers before me and of all of the women that they become. There are many women that live inside me and I honour them all.

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Ten years on into my sixties and I choose solitude as a partner. My life path is mapped from childhood.

Although alone, I am never lonely. The truth that I love and am loved springs from the heart of a family that tries its best, stumbles often, crawls along on its belly but stays true to love. I recall the mother of my mother, a tiny body filled with such fierce love, a longing to protect, the hunger to possess. I remember my mother and the bleeding heart she wears for a man who goes away. I see a worn wedding band that jumps from her finger at the instant of his death. I never find nor want such attachment. I have chosen for the most part to live alone.

I sit in my garden
red rose red breast
the raw and its roots -
the red and the reason

I permit myself now to live in the house of the mothers and I call it mine. I think increasingly about all of our lives, about their deaths, about time passing and my own death ahead of me. There comes a sweet memory of a dear face, bathed in pure light as the priest blesses her and my mother answers to him calmly that she is ready.

When, I wonder, will I be prepared?

I reflect on my own death. I have no daughter to watch the mother, so I will surely die alone. But I do not fear death. It is legacy from my mothers, that death in itself brings only release. It is living that hurts. Yet it is the losing of life unlived, that seems to me to be so unbearable. Those chances missed, things unsaid or unfinished, the lives we could or should have lived. I feel all of the living left inside of me and I fight against the loss of it. I rail against my frailty; there is much left to do and I am not ready to let go.

I delight in this garden, it is space for peace and purpose, a growing place, healing and alive. I spend hours sitting in silence, feel the wind shake through leafless branches, hear the bird calls on the air. I am no hearty gardener but I sift soil through my fingers and loosen flowers from the weeds that bind and choke,

I have chanced upon this rose, a single rose, red as blood, holding brave against the tangled green of a creeper that threatens to bury it. Will I prise the bloom free to breathe in the light of a winter morning and allow a gust of November wind to flutter its petals?

In my mind's fancy, this proud red rose is the soul of my mother, happy to see me at peace in her garden, dancing gaily with her pretty petals, so windswept and free.

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The robin visits each day and stays for as long as I need it. Within its song each dawn is the gentle reminder of rebirth, renewal and hope. Wise words say that if a redbreast visits often it is a loved one from Heaven reaching out; 'I'm with you, I am watching you and I will always love you.' The tiny robin that does not let me go is surely Mama, guarding me in her garden, ever ready to protect.

In order to tell my story as an older woman, the story of mothers and daughters, I have needed to hold all of our imperfections and not feel treachery where I have decided to tell to myself and to others a tale that is less than kind, in parts, although more loving than words can describe in others. Some details that I have uncovered for myself will stay untold. They need never be shared on this page or any place else. But the story, told or untold, is a heart story, a healing of the heart. And I owe it to us all.

Notes:

1 'the red and the reason' ... a phrase from *Rooms of Consequence* by survivor poet Louise Hunt (unpublished, 2017).

I acknowledge the importance of Louise Hunt's survivor poetry; it is from her that I lifted the phrase 'the red and the reason' and through her that I grew the courage to talk about myself tenderly and without shame.

And I celebrate the pioneering activities of two lived experience organizations, Making Waves UK and Nottingham MAD Network, where I continue to survive and thrive through their wisdom, support, and inspiration.



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Severe and enduring mental illness

Chapter: Severe and enduring mental illness

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Introduction

This chapter addresses the needs of people growing old with long-term, severe mental illness. This group comprises mainly people with schizophrenia and other psychotic mental illness, but also a smaller number with bipolar affective disorder and other diagnoses, including major depression, obsessive compulsive disorder, personality disorders, and substance misuse. Much of the clinical research, and therefore most of this chapter, concerns people living with schizophrenia or psychosis, but the service considerations also apply to those with these other diagnoses.

Moving from institutional to community care

In the nineteenth and for much of the twentieth century, people with long-term functional mental illness in the UK were cared for in large county asylums. Many other countries had similar arrangements. At the peak, in

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1955, there were 152,000 inpatient psychiatric beds in the UK. From the 1960s onwards, this model of care was questioned, as the disadvantages of long-term institutionalization became clear, so bed numbers were gradually reduced, with a shift of focus to care in the community. The old asylums have now been closed down.

Older people with chronic psychosis (sometimes referred to as 'graduates', since they graduated from one part of the hospital to another (Jolley et al., 2004) were among the last to benefit from this new approach. In 1975, just over half of the 41,864 people resident in mental hospitals in England for more than five years were aged 65 and over (Department of Health and Social Security, 1978). In addition to the impairments associated with their illness, they were further handicapped by their long hospital stay, which had left them with no independent living skills. Clifford and colleagues (1991), surveying the population of five hospitals destined for closure, found that of those with functional diagnoses hospitalized for over a year, the mean duration of admission was 24.5 years and their mean age was 64.5. Where hospitals were closed, the outcomes for discharged patients were reasonably positive, with more social contacts and higher levels of life satisfaction than people who had remained or been readmitted to hospital (Leff and Treiman, 2000).

The 1990 NHS and Community Care Act made local authorities responsible for providing appropriate community mental health services. This formalized the shift in attitudes over the preceding three decades. It was envisaged that people with chronic mental illness would live independently with support from community mental health teams and social care services and access mainstream education, leisure, and employment facilities. Unfortunately, not all of the expected benefits of community care have been realized. The promise of integration into the community was often not fulfilled and many former patients were merely 'transinstitutionalized' rather than deinstitutionalized, as they moved into nursing homes that differed very little from the wards from which they had come. Services were criticized for being fragmented and failing to meet need (Killaspy, 2006).

Numbers of mental health beds fell by 72.1% from 1987 to 2017. This compares to a 32% reduction in general and acute physical care beds (Gilburt et al., 2014). Lengths of hospital stay reduced but conversely readmission rates increased leading to the advent of the 'revolving door patient' (Jeppesen et al., 2016).

Some people with enduring mental illness have undoubtedly been diverted to the prison or homeless populations (Priebe et al., 2005). Crane and colleagues (2005) found that two-thirds of a sample of 219 homeless people aged over 55 from four UK cities had a mental illness and that, for at least 18% of them, it was a factor in their becoming homeless.

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Since the demise of the large institutions it has become more difficult to identify people with enduring mental illness, as they are scattered between different living situations and cared for by different services (if indeed they are receiving any service at all). This has led to them being almost invisible in terms of research and policy. For example, the NICE guidance on interventions and management of psychosis and schizophrenia (National Collaborating Centre for Mental Health, 2014) makes no specific mention of the distinct needs of older people.

Epidemiology

The adult psychiatric morbidity surveys in England found one-year prevalence rates for probable non-organic psychosis in those aged 65–74 of 0.2% using pooled data from the 2007 and 2014 surveys (this compares to 0.5% for those aged 16–74) (McManus et al., 2016). Similarly, in the US, the National Comorbidity Survey Replication also reported a lifetime prevalence rate of 0.3%, which fell to 0.1% among people over the age of 60 (Kessler et al., 2005). These figures are likely to represent an underestimate of the prevalence of older people with psychotic mental illness, both because of the exclusion of those living in institutional care and because even those living at home are unlikely to respond to surveys.

Smaller community surveys have given prevalence rates of 0.1–0.5%, including in Liverpool (Copeland et al., 1998), Camberwell, London (Castle and Murray, 1993), and Lanarkshire, Scotland (McNulty et al., 2003). Regional prevalence figures will be affected by the historical structure of services, in particular the presence of large asylums in some areas. Rodriguez-Ferrera and colleagues (2004) found approximately half the number of cases in rural Suffolk as McNulty and colleagues in Lanarkshire, and that a much higher proportion of subjects in their sample lived independently. They thought this was probably due to some patients having been placed in the county asylum and not returning to their original area.

Reported prevalence rates in older people are thus lower than the 1% lifetime prevalence usually quoted for schizophrenia overall. Some of the difference might be accounted for by incomplete ascertainment, but excess mortality due to suicide and physical ill health earlier in life are also major determinants.

Course and outcome of schizophrenia

The outcome of schizophrenia in older age is a contentious issue. Of necessity, the long-term studies needed to address this question encompass eras with differing diagnostic definitions, treatment options, and social contexts, and this makes their findings difficult to interpret. In addition, patients included in long-term observational studies have tended to be those institutionalized patients with a poorer prognosis.

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Despite these limitations, long-term outcome studies of patients in the US and Europe followed up over 22–37 years have consistently shown that approximately half to two-thirds of patients achieve significant improvement or recovery in the long term (Bleuler, 1972; Huber et al., 1975; Tsuang et al., 1979; Ciompi, 1980; Harding et al., 1987; Marneros et al., 1992). The WHO International Study of Schizophrenia (ISS) provides particularly powerful evidence as it included 1,633 patients from 18 centres around the world followed up over 15–25 years. Overall, 50% had a good outcome, increasing to 60% in some centres in low- and middle-income countries (Harrison et al., 2001).

Observed rates of recovery are dependent to a very large degree on the criteria used, specifically whether these are entirely symptom based or incorporate aspects of social functioning. The relationship of symptoms to function is not simple, as patients may develop coping mechanisms that allow improved functioning despite ongoing psychotic symptoms. There is good evidence to indicate that cognitive impairment is a better predictor of adaptive function than psychotic symptoms (Green, 1996; Velligan et al., 1997).

Andreasen and colleagues (2005) proposed consensus criteria for defining remission as the absence or low intensity of eight core positive and negative symptoms sustained for a period of at least six months. They distinguished this from recovery, which they conceptualized as a broader concept encompassing cognitive, functional, and social criteria. Recent studies employing these remission criteria in older patients have shown approximately 50% remission rates in two outpatient populations in the US (Bankole et al., 2008; Leung et al., 2008) but only 29.4% in a catchment area sample in the Netherlands containing both community-dwelling and institutionalized subjects (Meesters et al., 2011).

Cohen and Iqbal (2014) followed up 100 older people with schizophrenia from their New York cohort for an average of 4.5 years and found that 35% never attained remission and a quarter of patients relapsed during the follow-up period. However, a further quarter of patients remained in remission throughout the follow-up period and 16% of patients attained remission during that time.

A different approach to outcome is to ask people with schizophrenia about their subjective quality of life (QoL). Although there is no universally accepted definition of QoL, the WHO defines it as ‘an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations and standards’ (Saxena and Orley, 1997). Health-related quality of life (HR-QoL) refers to the impact of a disease on a person’s wellbeing. Studies have found that older people with schizophrenia have lower HR-QoL than community controls (Patterson et al., 1996a; Cohen et al., 2003). Depressive symptoms and cognitive impairment have consistently been shown to predict lower QoL (Cohen et al., 2003; Mittal et al., 2006; Meesters et al 2013). However, recent studies have

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suggested that mental health-related QoL actually improves with ageing despite reduced physical HR-QoL (Reine et al., 2005; Folsom et al., 2009). In a qualitative study, participants described reduced impact of symptoms and better self-management strategies with ageing (Shepherd et al., 2012).

Overall, it appears that while complete and sustained symptomatic remission is uncommon, this does not preclude a positive functional outcome (Cohen et al., 2008; Jeste et al., 2011). There may be even greater cause for optimism in the future as the cohort of people now entering later life with schizophrenia did not have the benefit of early recognition and effective treatment of their illness and were faced with even greater stigma and social exclusion than exists today. With reduced duration of untreated psychosis (Perkins et al., 2005) and avoidance of secondary disability, outcomes may improve still further for today's cohorts.

Cognitive impairment

Cognitive impairment has long been recognized as a major component of the clinical syndrome of schizophrenia. Although the impairments are global, semantic memory and executive functioning are the most prominently impaired cognitive domains (Heinrichs and Zakzanis, 1998).

Cognitive deficits are often present at first episode and indeed even predate the onset of illness (Jones et al., 1994), but whether these deficits remain static throughout life or continue to deteriorate over time remains controversial (Rund, 1998; Irani et al., 2011; Radhakrishnan et al., 2012). Cross-sectional studies of mostly younger community-dwelling patients with schizophrenia showed no deterioration in performance over time scales of up to ten years (Heaton et al., 1994; Eyler Zorilla et al., 2000), although they were significantly impaired compared to normal subjects. In contrast, studies of older institutionalized patients have shown deterioration over periods of less than three years (Harvey et al., 1999; Friedman et al., 2001). Studies of long-term institutionalized patients may be confounded by the effects of institutionalization itself, use of long-term psychotropic medication, and selection for those with a poorer prognosis.

Structural brain imaging studies consistently show a reduction in gray matter volume at first episode and ongoing gray matter volume loss over time, most marked in the frontal and temporal lobes (Vita et al., 2012). Meta-analysis of cross-sectional imaging studies across the lifespan suggests that the loss of grey matter plateaus in middle age but that white matter deterioration becomes apparent after age 35 and that this is accelerated in comparison to control subjects (Cropley et al 2017). Thus, there may be two distinct pathological processes that explain the early static cognitive deficits and the later cognitive decline observed in clinical studies.

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Pharmacological strategies to ameliorate cognitive dysfunction have not been successful to date. Antipsychotic medication has only a modest effect on cognitive impairment (Keefe et al., 2007), and apparent benefits are likely to be due to improvement in psychosis, rather than in cognition per se. Indeed, antipsychotic drugs often have sedative effects that would tend to impair rather than improve cognition. Furthermore, despite some early promise in open-label trials, cholinesterase inhibitors have not been shown to be effective in randomized placebo-controlled trials (Akhondzadeh et al., 2008; Lindenmayer and Khan, 2011).

Psychological and behavioural treatments, in particular cognitive remediation therapy, have demonstrated greater efficacy in clinical trials than drug treatments although the benefits remain modest (Wykes and Spaulding, 2011) and unfortunately, efficacy in older patients with longer duration of illness is reduced compared to early stage participants (Golas et al., 2015; Corbera et al., 2017).

Patients with schizophrenia have a two-fold increased risk of a diagnosis of dementia compared to the general population (Ribe et al., 2015). However, the underlying cause of dementia remains unclear. Older people with functional mental illness are no more likely to have the specific neuropathological brain abnormalities associated with Alzheimer's disease (AD) than the general population (Baldessarini et al., 1997; Arnold et al., 1998; Arnold, 2001) and even subjects with marked cognitive impairment do not show neuropathological abnormalities sufficient for a diagnosis of AD (Rapp et al., 2010). Similarly, cortical beta-amyloid levels are lower in schizophrenia than in AD, and do not correlate with cognitive impairment in patients with schizophrenia (Chung et al 2016). Nonetheless, given the high prevalence of AD, the two conditions can co-occur and it can be difficult to distinguish the cognitive impairments associated with schizophrenia from a new onset of dementia. Short-term memory loss, word-finding difficulties, and disorientation are more associated with AD, whereas frontal executive deficits are more associated with schizophrenia. The time-course of cognitive decline, along with evidence of decline in functioning, is also helpful in making the distinction.

Mental capacity

Lack of insight is very common in schizophrenia and can lead to difficult decisions about whether a patient has capacity to refuse care or treatment, and whether or when to intervene in a person's best interests. In England and Wales, the Mental Capacity Act 2005 provides a clear framework for making decisions. However, in the case of older people with functional mental illness, the decision often hinges on the complex issue of a person's ability to weigh evidence and make a decision rather than on simpler issues of understanding or retention of information. Impaired decision-making capacity is not by any means a universal finding. In one study, 69–89% of subjects with psychotic mental illness were able to score in the same range as control or medically ill subjects

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on a test of decisional capacity (Candilis et al., 2008). Cognitive impairment is the best predictor of impaired capacity, and understanding can be improved by repeating or simplifying the information presented (Moser et al., 2006; Palmer and Jeste, 2006), but these improvements tend not to be sustained in the long term (Wang et al., 2016).

Depression in schizophrenia

Approximately 60% of people with schizophrenia experience an episode of major depression during the course of their illness and around a quarter of them experience depression following an acute schizophrenic episode (Martin et al., 1985). Depression is associated with poorer outcomes, including poorer response to drug treatments, longer duration of inpatient care, chronic course, and increased rates of relapse and suicide (Cohen et al., 1996; Siris, 2000; Jin et al., 2001).

Two relevant studies (Diwan et al. 2007; Meesters et al., 2014) found significantly elevated rates of depression (32% and 47.5%, respectively) in community-dwelling older patients with schizophrenia compared to age matched controls (11% and 12.1%, respectively). In both cohorts, depression was significantly associated with physical illness and lack of confiding relationships.

Depression may be confused with the negative symptoms of schizophrenia but can be distinguished by the presence of low mood, early morning waking, and loss of appetite (Felmet et al., 2011). Although evidence is scant, there is reason to believe that treatment is likely to be successful. For example, a double-blind randomized controlled trial (RCT) of citalopram in 198 patients with schizophrenia and subsyndromal depression aged 40–75 demonstrated improvements in mood, social functioning, and QoL (Zisook et al. 2009; Kasckow et al., 2010).

Physical health

People with schizophrenia have a two- to threefold increased mortality rate compared to the general population (Laursen et al., 2012; Talaslahti et al., 2016) and on average their life expectancy is reduced by around 20 years (Laursen et al., 2014). Some of this excess mortality is due to suicide, but there is an increased risk of death from natural causes, including cardiovascular and respiratory disease, infections, and type 2 diabetes (Jeste et al., 1996; Brown et al., 2000). This is likely to be multifactorial and related to lifestyle factors, side effects of medication, and reduced access to healthcare (Laursen et al., 2012).

Patients with schizophrenia are more likely than the general population to have lifestyle risk factors for cardiovascular disease. They are more likely to smoke, less likely to exercise, and more likely to have high-fat, low-fibre diets, even when the study population is controlled for socioeconomic status (Brown et al., 1999; McCreddie et al., 2003; Osborn et al., 2008).

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Side effects of antipsychotic medication may also contribute to increased morbidity and mortality. The cardiovascular side effects of antipsychotic medication include lengthening of the QT interval, which may contribute to arrhythmia and sudden cardiac death (Glassman and Bigger, 2001). Significant weight gain, dyslipidaemia, and new onset of type 2 diabetes are particularly associated with newer atypical antipsychotic medications. Conventional antipsychotic medications may significantly elevate prolactin levels, which interferes with sexual functioning and reduces bone density, increasing the risk of osteoporosis.

Patients with schizophrenia are less likely to receive treatment for physical health problems (Kilbourne et al., 2008; Vahia et al., 2008). Data from the Patient Outcomes Research Team (PORT) study in the US (Dixon et al., 2000) showed that 30% of patients reporting a physical health condition were not receiving treatment. Mitchell and Lord (2010) showed that following a myocardial infarction, patients with schizophrenia were less likely to be offered revascularization procedures and less likely to receive optimum medication regimes. Similarly, Bergamo and colleagues (2014) showed that, despite presenting with earlier stage lung cancer than control subjects, patients with a diagnosis of schizophrenia were less likely to undergo appropriate evaluation or to receive stage-appropriate treatment. Their survival was decreased by on average four months but this difference disappeared when adequacy of treatment was controlled for.

People living with schizophrenia may lack the motivation to attend appointments, or cognitive deficits or delusional ideas may make it hard for them to comply with treatment plans, but it is also likely that negative attitudes of care providers towards those with chronic mental illness play a role. Studies have shown that GPs were less likely to offer screening for cardiovascular risk factors to people with schizophrenia than to those with asthma or another diagnosis (Roberts et al., 2007).

Medication

There is a very limited evidence base to guide antipsychotic treatment in older people as they are frequently excluded from large-scale RCTs. A 2006 Cochrane systematic review (Marriott et al., 2006) found only three RCTs conducted specifically in older patients with a total of 252 patients. One trial, comparing olanzapine with haloperidol in 117 patients aged over 60, found that olanzapine was both more efficacious and better tolerated than haloperidol (Kennedy et al., 2003). A further RCT comparing olanzapine and risperidone in 175 older patients with schizophrenia found no significant differences between the two treatments (Jeste et al., 2003). Older patients have been included in other trials, but the number of older subjects is either not specified or too small for meaningful subgroup comparisons.

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In very late-onset schizophrenia, the ATLAS trial (Howard et al., 2018) demonstrated a clear treatment benefit of low dose (100mg daily) amisulpride over placebo but the relevance of these results to patients whose onset of psychosis was earlier in life is unclear. However, Pridan and colleagues (2014) conducted a retrospective survey of 30 elderly patients with early onset schizophrenia treated with amisulpride monotherapy and found that it was well tolerated, the mortality rate was significantly lower than that of other first- and second-generation antipsychotics (10% vs 19%), $P < 0.02$) and rehospitalization rates with amisulpride were also significantly lower than those with other second-generation antipsychotics ($P < 0.001$).

Clozapine is the only antipsychotic medication shown to have greater efficacy in treatment-resistant schizophrenia (Kane et al., 1988) and has negligible risks of tardive dyskinesia (TD), but its use is tightly controlled due to rare but serious adverse effects including agranulocytosis, cardiomyopathy, and seizures. More common adverse effects include sedation and postural hypotension. There is very little evidence to guide its use in older patients and this is likely to become an increasingly important issue, as patients who were prescribed clozapine for treatment-resistant schizophrenia as young adults age.

One RCT comparing clozapine with chlorpromazine in patients over 55 found no differences between the two drugs (Howanitz et al., 1999). Barak and colleagues (1999) reviewed the literature and identified 139 reports of patients aged over 65 treated with clozapine for a psychiatric indication. The mean dose used was 135 mg. Clozapine was discontinued in 25% due to side effects, noncompliance, or inefficacy and the rate of leukopenia was 5%. Pridan and colleagues (2015) identified 43 elderly patients (mean age 69.4 ± 8.7 years) with treatment-resistant schizophrenia prescribed clozapine in a retrospective chart review. Clozapine was very well tolerated and the mortality rate was not significantly different from that of patients prescribed other first- and second-generation antipsychotics (18.6% vs 18%); however, rehospitalization rates with clozapine were significantly lower than rates for the five-year period prior to exposure to clozapine (0.41 vs 3.8; $p < 0.001$).

However, in actual practice, rates of stopping clozapine among older patients with schizophrenia seem quite high, mainly due to side effects (Snowdon and Halliday, 2011). Overall, the evidence suggests that clozapine is effective and reasonably safe in older people if it is used and monitored carefully (Bishara and Taylor, 2014).

Older patients usually require lower doses of medication due to physiological changes associated with ageing (see Chapter 13). For example, there is an increase in the proportion of body fat with ageing, which increases the volume of distribution of lipid-soluble drugs and prolongs their action; glomerular filtration rate decreases, reducing clearance of renally excreted drugs such as lithium; and liver metabolism

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may also be reduced, leading to increased plasma concentration of drugs such as benzodiazepines.

In clinical practice, one is often faced with the dilemma of weighing up whether to reduce antipsychotic doses as patients become older and frailer versus the risk of relapse of psychotic symptoms in someone who may have been stable for many years. There is little research evidence to guide decision-making, but Harris and colleagues (1997) found that it was possible to reduce antipsychotic medication doses by about 40% in a sample of patients aged over 45 without an increase in symptoms.

A different approach to evaluating dose reduction has come from PET imaging studies (Graff-Guerrero, et al., 2015). In an open label trial, 35 older schizophrenic patients on a stable treatment dose of olanzapine or risperidone underwent PET scanning to determine striatal dopamine D2/3 receptor occupancy before and after a gradual dose reduction of up to 40% from their baseline antipsychotic dose. The lowest D2/3 receptor occupancy level associated with clinical stability was 50%.

Extrapyramidal symptoms (EPS) were more likely to occur with D2/3R occupancies higher than 60%. This suggests that the therapeutic window of striatal dopamine D2/3 receptor occupancy in older patients with schizophrenia is lower than the 65%–80% typically reported in younger patients.

These studies support a strategy of gradual dose reduction over time. How rapidly this is done depends on various factors, such as the potential severity of relapses, and also on the wishes of the patient, as some people will be more cautious about going on to a lower dose than will others. It is also often possible to replace depot injections with oral medication, especially if the person with schizophrenia is starting to receive personal care. This obviously makes it easier to assess the effects of altered dosages.

Older people are more susceptible to side effects from medication. Tardive dyskinesia (TD) is a particular problem with typical antipsychotic medications such as haloperidol and the risk is five to six times higher in older patients (Jeste, 2004). Studies of older hospitalized patients have shown very high rates of TD of 60–90% (Quinn et al., 2001). TD is often irreversible even after stopping medication, and although patients are usually not aware of the movements, they are obvious to others and can be stigmatizing. In severe cases, TD can cause difficulties with eating and swallowing.

Other common side effects are those related to anticholinergic actions, such as cognitive impairment (Tsoutsoulas et al., 2017), constipation, and urinary retention. All of these can be more severe in older people due to the interaction with physiological ageing and the concomitant use of other medication with anti-cholinergic properties. For example, prostatic hypertrophy in older men puts them at higher risk of urinary retention. In some cases, different side effects combine to increase the risk of an

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adverse outcome, e.g. antipsychotic medications cause both orthostatic hypotension, which can lead to falls, and reduced bone density, which increases the risk of fracture. Older people are also likely to be taking multiple physical health medications and this increases the potential for drug interactions.

Nonpharmacological treatments

There is now considerable evidence of benefit from cognitive behavioural therapy (CBT) in younger patients with schizophrenia (Tai and Turkington, 2009). CBT is recommended by NICE (National Collaborating Centre for Mental Health, 2014) for improving persistent psychotic symptoms and increasing insight and treatment adherence and it can be delivered in one-to-one sessions with a psychologist or in a group. Other psychological therapies, such as social skills training and cognitive remediation, have also been shown to be valuable in younger adults. Skills training is usually undertaken in a group and may include learning about verbal and nonverbal communication and rules of social interaction using role play and exercises.

The effectiveness of combined interventions including elements of these therapies has also been evaluated. Patterson and colleagues (2006b) developed functional adaptive skills training (FAST) and evaluated it in an RCT in 240 patients aged over 40. They showed significant improvements in social skills and activities of daily living and reduced use of emergency services in the intervention group. Granholm and colleagues (2005, 2007) also used a group cognitive behavioural and social skills training intervention (CBSST) in 76 older outpatients with schizophrenia or schizoaffective disorder, and showed significant improvements in social function and insight that were sustained over a year despite no improvement in symptoms.

In summary, the evidence suggests that older people are able to benefit from psychological therapies, but sadly, in clinical practice these interventions are not yet widely available to older people.

Social functioning

People with schizophrenia are less likely to marry and have children than the general population. About two-fifths never marry and a further quarter are divorced. Two-fifths do not have children (Cohen and Talavera, 2000). They are also less likely to have been in employment and their lives may be disrupted by substantial periods of hospitalization. All of these factors lead to them having substantially reduced social networks. Of those contacts that they do have, most are based on provision of sustenance or support (59% vs 15% for age-matched peers) and few are intimate, confiding relationships (44% vs 67%) (Cohen et al., 1996).

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On measures of social skills, they are significantly impaired in accepting and initiating contact with others, group participation, and making friendships (Bartels, 1997b). Social withdrawal may be a mechanism to cope with distressing psychotic symptoms, such as persecutory delusional beliefs or thought interference, or may result from reduced capacity to enjoy friendships due to negative symptoms.

Despite these deficits, older people with enduring mental illness do identify social needs as important. Auslander and Jeste (2002) examined the self-reported needs of a sample of 72 people (41–80 years). Around half of them lived independently and the remainder (47%) lived in an assisted care facility. The study excluded people with dementia or with a comorbid alcohol or substance abuse problem. The main priorities they identified were around social relationships (developing and sustaining friendships), managing their illness, and improvements in mood, physical health, and memory.

Accommodation

With the decline of long-stay wards and psychiatric hospitals, other types of provision have arisen to fill the void. Hostels and care homes run by private sector and voluntary organizations vary from those with 24-hour staffing by qualified staff to those with daytime cover only from a smaller number of staff without specialist qualifications. Group homes are unstaffed facilities where small groups of residents with chronic mental illness live together supported by visits from staff (Macpherson et al., 2004). A more recent model of care is where each individual has his or her own flat or bedsit but within a unit where there is a staff member present and often some communal facilities. There is evidence that this form of support is preferred by patients (Tanzman, 1993).

Many people with enduring mental illness live with their families. Tsai and colleagues (2011), examining data from the large Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study of outpatients aged 18–65 with schizophrenia in the US, found 46% living with family members (vs 18% living independently, 17% in an institution, and 14% with no stable housing). There are no corresponding national data for older people. These percentages are likely to vary depending on cultural expectations and on provision of alternative resources.

Homelessness is also a significant issue for people with enduring mental illness. Around half of the homeless population is aged 50 plus (Lee et al., 2016) and rates of physical and mental illness are high. It is also important that providing a home for someone is more simply having a roof: elements that create a sense of 'home' are also needed (Ogden, 2014).

As people with enduring mental illness become older, physical disabilities or loss of support networks may mean that their needs can no longer be met in their previous setting. Andrews and colleagues (2009) studied

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admissions to nursing homes over a ten-year period in New Hampshire in the US. They found a much younger age of entry to a nursing home among those with a diagnosis of schizophrenia (65 vs 80 for those with no mental illness). The rates of admission started to diverge significantly between the ages of 40 and 65 where nursing home admission risk was 3.9 times greater than for peers with no mental illness. The reasons for this are not known, but one could speculate that loss or burnout of the primary carer may have contributed. Bartels and colleagues (1997a) found that cognition, functioning, and behaviour were important predictors of nursing home as opposed to community residence, with cognitive impairment especially important as it was also a predictor of a person's level of functioning. Auslander and colleagues (2001) also found that, among older patients with schizophrenia (age range 40–97), residence in assisted living facilities was associated with never having been married, the presence of cognitive impairment, and poorer quality of wellbeing.

Because their numbers are relatively small, those with functional illness are often placed in settings designed mainly for people with severe dementia that may be inadequate to meet their needs. Opportunities for social interaction and participation in particular are likely to be severely limited and freedoms curtailed. These problems might be overcome by better staff education and individual care planning and risk assessment.

Psychiatric services

There has been much debate about who should provide mental health services to older people with functional mental illness. Patients may continue to be provided for by general adult or rehabilitation services indefinitely or they may automatically 'graduate' to the older people's service on attaining the age of 65. People growing older with functional mental illnesses may perceive a great injustice in being discharged from services they have previously been able to access due to an arbitrary age cut-off of 65 years. Older people's mental health services are often more poorly resourced than rehabilitation services for younger adults and focused around dementia, rather than functional illness. Access to services such as crisis resolution and home treatment teams for acute relapses or assertive outreach teams may be restricted to working age adults. On the other hand, older people's services may be better placed to meet the needs of those with physical frailty or cognitive impairment, whatever their age.

As discussed in Chapter 20, there has been a threat to merge old age psychiatry services into generic 'age inclusive' services. This has led to the development of criteria for old age psychiatry services that are based more on clinical need than on chronological age (RCPsych, 2015; Royal Australian and New Zealand College of Psychiatrists, 2015; see Box 20.3 in Chapter 20). People with enduring mental illness therefore should remain within general adult services, unless i) they have been stable for some time and not in contact with specialist services, or ii) they have

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physical health problems that make old age services more appropriate, or
iii) they develop dementia.

Abdul-Hamid and colleagues (2015) conducted a survey of the needs of 74 elderly patients with functional psychiatric disorders in one urban area. Although total needs were not significantly different between those managed by old age and general adult services (8.0 vs 6.5 respectively) the participants in contact with old age psychiatry had significantly fewer unmet needs compared with those in contact with general adult psychiatry (2.8 vs 5.6, $P < 0.03$). Current UK mental health policy (NHS England, 2016) recognizes the evidence for specialist old age psychiatry services and states that 'bespoke older adult services should be the preferred model until general adult mental health services can be shown to provide age appropriate care'.

People with an enduring mental illness have often had many difficult experiences, and this may include their previous contacts with mental health services. Over the years, they may have experienced deprivations of liberty, invasive treatments, traumatic experiences, a lack of autonomy, and discriminatory attitudes. A personal history of this kind can increase their mistrust of healthcare professionals, and make them unwilling to seek help or remain in contact.

Future challenges

As the population ages, the numbers of people surviving into old age with enduring mental illness will increase (Cohen et al., 2015). However, the numbers will always be relatively small in comparison to those with dementia, who form the majority of patients of old age psychiatry services.

There are specific areas of expertise in working with older patients with long-term functional mental illnesses, e.g. around prescribing, medical support, housing and accommodation, and productive activities. Staff working within older people's mental health services need to have access to appropriate training and resources to develop and maintain their expertise. This needs to be recognized in planning and providing services, with suitable arrangements for staff support and supervision.

The lack of research in this age group means that there is a dearth of good quality evidence to guide practice. More research in particular into medication, psychological therapies, and services is urgently needed.

Conclusion

Older people with enduring functional mental illness represent a vulnerable, marginalized group in society. In addition, many have no family members or friends to act as advocates or supporters. They may be the victims of a double discrimination on the grounds of age and mental illness and are likely to receive poor quality care despite having high

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needs. It is important that current emphasis on other disorders, especially dementia, does not cause this group to be neglected.

Older people with enduring mental illness need access to good physical and mental healthcare, including screening and health promotion, given their high risk of physical ill health, psychiatric comorbidity, and drug side effects. Despite these challenges, positive outcomes are possible and older people should not be excluded from provision of innovative service models and psychosocial interventions.

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Alcohol and substance misuse

Chapter: Alcohol and substance misuse

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Introduction

The misuse of alcohol and other substances has increased noticeably in older people over the past decade, influenced by the cohort of 'baby boomers' born between 1946 and 1964 (Rao et al., 2015); with the oldest within this cohort crossing the age of 65 in 2011. In Europe and the UK, the number of people over 65 with a substance use problem, or needing treatment for substance misuse is expected to more than double between 2001 and 2020 (European Monitoring Centre for Drugs and Drug Addiction, 2008). In the United States, the number is expected to treble over the same time frame (Colliver et al., 2006). In Europe, the proportion of the population aged 65 or above is projected to rise to 25% by 2050 (European Monitoring Centre for Drugs and Drug Addiction, 2008), so the inevitable rise in older people with alcohol and substance misuse has implications for both the public mental health of older people and for old age psychiatry. The traditional definition of older people has been those aged 65 and over in the UK, but there may be grounds for including those

Alcohol and substance misuse

people over the age of 40 who have misused illicit drugs as they may show evidence of accelerated biological ageing affecting the brain and adverse psychosocial factors (Beynon, 2009). This is mainly because the length of time misusing opioids is often longer than the time spent misusing alcohol in this population and these drugs can exacerbate cardiovascular risk and accelerate premature ageing in other body systems (Beynon, 2009). Adverse psychosocial factors only add to this risk (Bachi et al 2017).

Alcohol and substance misuse in older people present many challenges and degrees of complexity that compound existing difficulties in the assessment, treatment and recovery of older people.

These include co-existing mental disorders (dual diagnosis), physical health problems and psychosocial factors such as retirement, bereavement and social isolation (Rao and Crome, 2016). Ageing also brings with it an increased likelihood of polypharmacy. Drugs available on prescription may be taken for non-medical reasons and those commonly misused include opioid-containing pain-relieving drugs, as well as sedative, hypnotic, and anxiolytic drugs.

This chapter discusses the following areas of alcohol and substance misuse in older people:

- Epidemiology and demography of substance misuse in older people
- Terminology of substance misuse in older people
- Public health and policy
- Examining evidence for benefits of substance use in later life
- Risk factors for substance misuse in later life
- Detecting substance misuse
- Taking a substance misuse history in an older person
- Clinical diagnosis and problems with using current systems
- Assessment of comorbidity
- Drug interactions with substances
- Treatment of substance misuse in older people
- Specific treatment approaches
- Driving and substance misuse
- Developments in policy and practice
- Conclusions and future directions

Epidemiology and demography of substance misuse in older people

The past decade has seen a sharp escalation in morbidity and mortality from alcohol misuse in older people in developed countries. In the UK over the past ten years, there has been a 22% reduction in the proportion of people aged 16–24 who drank any alcohol over the previous week,

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compared with a 3% increase for older people (Office of National Statistics, 2017). Over the same time frame, there was a 27% increase in the proportion of younger people who were teetotal, compared with an 18% decrease for older people.

Older people in the UK also showed an increase in exceeding recommended drinking limits on any one day over the previous week, with a 20% increase for older people (from 29% to 35%) compared with a 19% decrease from 72% to 59% for people aged 16–24 (Office of National Statistics, 2017). Between 2015 and 2016, older people formed 20% of hospital admissions related primarily to alcohol (Public Health England, 2017). This has increased by over 40% from 14% between 2010 and 2011. Although the age group at highest risk of alcohol-related deaths in men and women is people aged between 55 and 64 (Office of National Statistics, 2017), this group represents a cohort of ‘baby boomers’ who will soon start to move into the care of old age psychiatry services (Rao et al., 2015).

For older people in acute hospital settings, alcohol misuse is present in 40% of referrals to old age liaison psychiatry services (Rao, 2013).

In the United States (US), the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) found that between 2001–2 and 2012–13, people aged 65 and over showed the largest rises in the prevalence of 12-month alcohol use, 12-month high risk drinking and 12-month alcohol use disorder (Grant et al., 2017). Similar findings arose from the Australian National Drug Strategy Household Survey (NDSHS), with people aged 50 and over showing the highest rises in the prevalence of exceeding daily recommended guidelines, high risk and very high risk drinking (Australian Institute of Health and Welfare, 2017).

In the UK, 11% of men and 10% of women aged 60 and over smoke tobacco (NHS Digital, 2017). Over the past ten years, the prevalence of smoking in men over 60 has not changed, but it has decreased by 23% in women in this age range. Age is shown to be no barrier to stopping smoking: people aged 60 and over have the same quit rate of 28% as those aged 18–34 (NHS Digital, 2017).

Lifetime use of illicit drugs in older people has shown a sharp increase over the past 15 years. The Adult Psychiatric Morbidity Study (NHS Digital, 2016) showed the lifetime rate of cannabis misuse rising from 0.9% in 2000 to 6.8% in 2014. For amphetamines and cocaine, this has risen from 0.1% to 0.6%. In the United States, self-reported cannabis misuse in older people over the previous 12 months rose from 0.15% in 2003 to 2.04% in 2014 (Salas-Wright et al., 2017); in Australia, it rose from 1.5% in 2004 to 3.6% in 2013 (Kostadinov and Roche, 2017).

With increasing longevity, there is an increasing risk of prescription medication misuse in older people. This refers to inappropriate dose prescribing in dose, duration, or clinical indication. Such inappropriate

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prescribing occurs in up to 20% of older people, with opioids and benzodiazepines being the most common drugs implicated, both of which have the potential for misuse (Gottlieb, 2004; De Wilde et al., 2007).

Given the rise in the use and alcohol and other substance misuse in older people, the impact on public health and clinical services will need to be met by the provision of integrated care. Such service provision remains sparsely distributed (Rao and Shanks, 2011).

Terminology of substance misuse in older people

In this chapter, the term 'substance' refers to any psychoactive drug that acts on the brain to alter mood, thought processes, or behaviour. The term refers to licit drugs such as tobacco and alcohol, as well as illicit drugs such as opioids, cannabinoids, stimulants, lysergic acid diethylamide (LSD), khat, magic mushrooms, and novel psychoactive drugs. The term is also used to describe 'street' use, use of prescription drugs (e.g. benzodiazepines and opioids) in a manner not indicated or intended by a medical practitioner, and similar use of over-the-counter preparations, such as codeine-based products or drugs bought over the Internet (Royal College of Psychiatrists, 2011).

The chapter covers the most common drugs of misuse, which are alcohol, tobacco, opioids, benzodiazepines, and 'Z drugs' (the hypnotics zaleplon, zolpidem, and zopiclone), although the rising use of cannabis and gabapentinoids mean that these substances are also covered briefly. The term 'polysubstance misuse' is more commonly applied to the misuse of multiple illicit substances with or without coexisting alcohol and tobacco misuse; mostly by younger people who continue this misuse into later life.

The term 'polypharmacy' refers to prescribed drugs with the potential for interaction with each other and commonly refers to the misuse of drugs for pain (opioids); benzodiazepines and Z drugs for insomnia; as well as gabapentinoids for neuropathic pain and anxiety. All these drugs may also interact with alcohol and other illicit substances. The further potential to interact with other prescribed medication and with comorbid mental and physical disorders presents challenges to the overall management of substance misuse in older people (Rao and Crome, 2016).

Occasionally this chapter references early onset (EO) or late onset (LO) substance misuse. The concept of EO and LO problems was introduced by Atkinson and colleagues (1985) to distinguish between two different types of people with alcoholism (now known as Alcohol Use Disorders, AUDs) aged over 60 in a veteran alcoholism outpatient treatment programme (Atkinson, 1990). According to their criteria, EO refers to a drinking problem that occurred before the age of 40, while LO refers to problems that emerged after the age of 40 or 50.

This distinction is relevant because different risk factors are relevant for patients with EO or LO, and people with LO AUDs have a different prognosis to those with EO (Royal College of Psychiatrists, 2011). There

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is no formal dichotomy or research for other forms of substance use, such as cannabis or prescription medication.

People with EO are similar to younger people who misuse substances. Factors associated with EO include: on-going or persistent use of alcohol throughout adult life, family history of alcoholism (genetic link) and current psychological instability, particularly major affective disorders (e.g. major depression or bipolar disorder).

People with LO problems make up approximately a third of people with alcohol problems in later life (Mellor et al., 1996). People with LO present differently with no family history and greater current psychological stability. Onset of problems can usually be linked to a specific life event such as recent bereavement, retirement, or decline in physical health (Hurt et al., 1988).

Public health and substance misuse in older people

The earliest public health interventions for substance misuse were based around reducing harm from tobacco smoking, with approaches such as restricting advertising, raising tobacco taxes, banning smoking in public places, health warnings, and plain packaging for cigarettes, and the alternative use of electronic cigarettes to deliver only nicotine. Many of these interventions have already been implemented (Givel, 2015), but improving smoking-related health outcomes has been more effective in higher- and middle-income countries (Chow et al., 2017).

However, addressing alcohol-related harm in older people has been relatively more problematic (Royal College of Psychiatrists, 2011). Older people often reduce or stop their drinking if their health declines. People with poor physical health (a group sometimes referred to as ‘sick quitters’) may bias studies that look at the health outcomes of teetotallers or very light drinkers. Under-reporting in heavy drinkers may also distort the figures. The overall impact may be a false positive finding of ‘protection’ against poor health status in older people drinking within low-risk limits (Stockwell et al., 2016; Naimi et al., 2017). With attrition of younger heavy drinkers through alcohol-related mortality, older drinkers may also represent a group that is healthier than the overall older drinking population, who may be less susceptible to the adverse effects of alcohol. This has led to the observation that regular alcohol consumption in later life is an indicator, rather than a cause, of good health (Holdsworth et al., 2016).

This finding is compounded by variable definitions of what constitutes a ‘drink’, with the UK being the only country that refers to ‘units’ (1 UK unit equals 8 g of pure alcohol). However, there has been a recent revision as to what constitutes ‘low-risk’ drinking, with the UK now defining this as being no more than 14 units of alcohol per week for both men and women of all ages (Department of Health, 2016). This might not apply to older people, where the physical effects of alcohol are more

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likely to be affected by an increased fat-to-water ratio, interaction with prescription medication, and comorbid mental and physical disorders such as dementia, higher vascular risk, and reduced metabolism of alcohol and other substances. For this reason, it has been suggested that the UK adopt US guidelines of no more than 7 US drinks (12 UK units) per week for older people (Royal College of Psychiatrists, 2015).

In the UK, public health functions and those functions previously held by the National Treatment Agency were formally transferred in 2013 to Local Authority Health and Wellbeing Boards. This has now brought the responsibility for commissioning substance misuse and health promotion services under Directors of Public Health, rather than addiction services.

Examining evidence for benefits of substance use in later life

Despite government guidelines for low-risk drinking and greater knowledge about the risks of drinking, alcohol is pervasive in UK society and people receive mixed messages about the benefits and risks of alcohol use. Older people who have been drinking for longer are likely to hold certain opinions or attitudes about alcohol. They may also selectively draw on any positive messages about putative benefits of alcohol.

To support people to make sensible cost-benefit judgments about the risks of alcohol (and other substances) compared to the perceived benefits, it is important for practitioners and the public to be informed about the latest evidence.

Overall health: The 'U' or 'J' shaped curve

As described previously, a common message both in the research literature is that 'teetotallers' (e.g. those who abstain from drinking completely) have higher morbidity and mortality than those who drink moderately. This is usually described as a 'U' or 'J' shaped curve. There is now an argument that regular drinking in later life is an indicator of good health, rather than the other way around.

Using data from the English Longitudinal Study of Ageing (ELSA), Holdsworth et al (2016) found that older people with poor or fair self-rated health at the start of the study drank less frequently compared to those with good health. They concluded that messages should be revised about the benefits of moderate drinking in later life. The limitations of these interpretations have been mentioned previously.

Cardiovascular health

The cliché 'red wine is good for your heart' is sometimes quoted by people as a reason for continued consumption. This idea often features in media coverage about the issue (Szmitko and Verma, 2005). The origin of this message was the findings of the Copenhagen City Heart Study (a large longitudinal study observing 13,285 men and women for 12 years). Drinking red wine benefited cardiovascular health compared to drinking

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beer and spirits, with wine-drinkers having half the risk of dying from coronary heart disease (CHD) or stroke compared to those who never drank wine (Truelsen et al., 1998). It was speculated that antioxidants and flavonoids in red wine protect against CHD and some cancers (Hertog et al., 1993).

If a patient says they drink red wine for health reasons, it should be communicated that the evidence is not strong enough to encourage patients to *take up* red wine as a strategy to reduce the risk of heart problems (Szmitko and Verma, 2005). A discussion with this patient could include helping them understand the evidence, particularly that other factors related to wine consumption are likely to play an important role in heart health (such as diet, exercise, or socioeconomic status).

Cognitive function

A concern when using substances in later life is whether sustained use has an impact on cognitive functioning, and what level of consumption may be harmful. This can be particularly concerning to older people given the coverage about dementia. There is some evidence to suggest alcohol can benefit cognitive function. For example, Reas and Laughlin (2016) found that compared to not drinking, or drinking less frequently, moderate regular alcohol intake (in this case meaning 3–4 drinks per day, a ‘drink’ classed as a 12-ounce glass of beer, a 5-ounce glass of wine, or 1.25 ounces of spirits) in people aged 51–99 was associated with better cognition (including executive function and visual memory) than lifetime abstainers or former drinkers.

However, despite some evidence showing protective effects, the impact of excessive drinking across the lifespan on cognitive function in later life is unknown. Damage to the brain as a result of heavy alcohol consumption may appear in a ‘dose-dependent fashion, leading to raised triglycerides, hypertension and other factors, which could contribute to adverse cerebrovascular changes’ (Gupta and Warner, 2008).

Most studies that do find positive benefits of moderate intake of alcohol in an older age group do not suggest people should be encouraged to take up drinking to improve their health. Advice to older people about how much alcohol may be ‘safe’ or ‘beneficial’ for them will depend on diagnoses of other problems (see Alcohol-related brain damage section for more information).

Risk factors for substance misuse in later life

Certain individual and sociocultural risk factors may influence substance misuse in an older age group. Psychosocial factors include: retirement, financial situation, peer influence, marital status, and level of social support. Individual factors include gender and coping strategies. These factors may influence assessment, treatment planning, and effectiveness of treatment.

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Psychosocial factors

Retirement is a transition that typically occurs later in life. It can be a risk factor for substance misuse due to: more free time, more financial resources, boredom, loss of identity, lack of structure, and frustration with expectations versus the reality of retirement (Kuerbis and Sacco, 2012; Bamberger, 2014). Wang (2007) found that retirement transitions can be particularly difficult for those in poor health, as they do not get to enjoy meaningful activities with their new free time. Bamberger (2014) suggested it is the nature of the retirement period (e.g. deferring retirement or being forced to take early retirement) or a lengthy or stressful transition period that can increase risk of alcohol problems.

A person's financial situation can influence alcohol or substance consumption through availability and access. People receiving a generous pension may have accumulated savings or acquired financial assets over time, and may be able to afford to consume alcohol or other substances more frequently. Availability or access to alcohol in particular may be less of an issue in later life than in younger years as a person may have alcohol in their home, and family members may buy alcohol for them.

Older people have more access to prescription medication, either their own or acquired from their partner or friends.

Peer influence or 'peer pressure' is still perceived as a risk factor for substance misuse in certain groups in later life. Sacco and colleagues (2015) found alcohol use was influenced by both peer consumption and availability in a retirement community, with heavy drinkers having a different social network than those who abstained. When taking a social history, the continuing influence of others and opportunity to consume should be considered. The exploration of normative drinking patterns in current peer group is useful. Identifying specific 'at risk' times such as extended holidays or social events can also be important for treatment planning or brief advice.

Marital status affects intake of alcohol or other substances. People most at risk of alcohol misuse are those who live alone, are widowed, separated, or never married (Holley-Moore and Beach, 2016). Recent bereavement, particularly loss of a spouse, can be a trigger for new alcohol or substance problems, or contribute to relapse. Perreira and Sloan (2001) found that widowhood increased alcohol consumption.

Older men appear to be at particular risk of depression, substance misuse, and suicide after bereavement (Brennan and Moos, 1996). A person's marital biography will interact with their substance use history and should be explored in assessment.

There is evidence for gender differences, for example, recent divorce increases men's, but reduces women's, alcohol use. There is evidence

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that re-marriage reduces alcohol consumption in men (Reczek et al., 2016).

Social isolation (defined as having minimal contact with others) and loneliness (defined as a gulf between level of desired and actual contact with others) has an impact on the physical and mental health of older people (Ong et al., 2016), and loneliness crosses over with risk factors for substance misuse.

Older people who say they are lonely are more likely to be female, divorced or widowed, have worsening physical health, and have little contact with friends or family (Pinquart and Sorensen, 2003). Social isolation and loneliness increase the risk of harm from substance use as older people are already more likely to drink alone, and to drink at home, than a younger group, which may mean fewer people looking out for the person or monitoring their consumption (Sacco et al., 2015).

Loss of spouse may also mean less responsibility, and less pressure to cut back. Older people living alone and drinking at home have an increased risk of falls. When discussing loneliness on assessment, an exploration of the breadth and quality of the person's current social network should be elicited. Family involvement in treatment can be important for recovery.

Individual factors

Gender

Older men are more likely to have substance problems (Atkinson, 1990), with 10% of men reporting heavy drinking at some point during their lives (Center for Substance Abuse Treatment, 1998). However, Epstein and colleagues (2007, p. 31) noted, 'the number and impact of female problem drinkers is expected to increase over the next 20 years', and we do not have the treatment services or assessment tools to be prepared for this. Between 1994 and 2012, the proportion of people aged 65–74 in the UK drinking above recommended daily limits increased from 5.3% to 14%, and from 6% to 14.8% in those aged 75 years or more, with increases greatest among women (Knott et al., 2015, p. 2).

An area of consideration when assessing an older female patient may be role changes, particularly loss of parental role or widowhood. Women may be at greater risk as they are more likely than men to outlive their spouses, and life transition changes increase the risk of LO alcoholism for women. Women have a higher risk of abuse of over-the-counter or prescription medications than men, and older women are more likely to be prescribed benzodiazepines (Blow and Barry 2012; Blow, 1998).

Coping with emotional problems

Emotional problems and depression can trigger and/or worsen problems with substance misuse in older people. Older people may be more vulnerable to experiencing emotional adjustment difficulties due to

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factors we have already explored (e.g. adjustment to physical changes or mobility, bereavement, and retirement). People who said they are not coping with the stresses in their life were five times as likely to be higher risk drinkers as people who say they coped well (Holley-Moore and Beach, 2016). In the same survey, high-risk drinkers were more likely to say they drank when feeling down or depressed, with only 1% of low-risk drinkers giving this reason. People who felt they had accomplished less than they would have liked to, or felt downhearted or depressed, were nearly four times more likely to be a high-risk drinker. Older people are at risk of using alcohol and other substances as self-medication.

Detecting substance misuse

Identifying substance misuse problems may be complicated by various barriers, which include individual, social and professional factors. Cognitive problems and the symptoms of other medical conditions may make it harder to detect possible substance misuse. Older people may be reluctant to discuss or disclose issues due to embarrassment or shame.

Societal barriers to screening include: ageism, attitudes and assumptions of society (e.g. that older people don't drink or take drugs), lack of appropriate research, and an emphasis on young people's substance use. Professional barriers include individual practitioner factors such as discomfort with raising the topic and failure to recognize symptoms, and organizational factors include a lack of guidance and support around this topic. This lack includes clinical guidelines, diagnostic criteria, suitable detection tools for older adults, and training opportunities.

It should be noted that people with LO problems may be quite difficult to identify. These patients tend to present 'well', and issues about substance use up until now may have been hidden. They may not have discussed drinking or drugs with anyone before (Center for Substance Abuse Treatment, 1998), so they may be embarrassed or inclined to deny any issues. For these people, questions about onset of the problem (including assessment of a recent bereavement or other significant life event), and family history will be important when considering reasons why the person is misusing alcohol or other substances. This information will also be helpful when making treatment recommendations.

To improve detection, and to provide some structure for assessment, there several tools available to assist the assessment of substance use disorders in an older age group (focusing on AUDs).

Table 46.1 provides a comprehensive review of the available alcohol assessment tools, outlining the advantages and disadvantages of each. Tools may be used alone or in combination to complement one another. They may also be selected depending on the context of the assessment, or how long you have with the patient.

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Table 46.1 Assessment tools available for detecting alcohol use disorders in older adults.

Clinical assessment using alcohol history		
Main Features	Advantages	Disadvantages
Ask patient if they have consumed alcohol within past three months. If yes, take a full alcohol history A cut-off of 14 units for older men and women showed a sensitivity of 0.92 and specificity of 0.98 for identifying problem drinking and consumption of alcohol on three or more days per week was also associated with high risk of adverse consequences (Mears and Spice, 1993)	Easy to do as part of clinical assessment May be more sensitive than some of the available screening methods, e.g. CAGE and laboratory testing (Mangion et al., 1992)	Not structured and relies on skill of clinician
Screening Questions		
Main Features	Advantages	Disadvantages
'On any single occasion during the past three months, have you had more than five drinks containing alcohol?' (Taj et al., 1998) Two single-item screeners (Dawson et al., 2010): Past year frequency of drinking 5+/4+ drinks on one occasion and maximum drinks	Useful starting point if risk of harm at lower levels of alcohol consumption is considered Accurately identifies patients at risk or who meet accepted criteria for alcohol abuse or dependence Simple to administer and quick to do Preferred by primary care	These studies did not specifically look at an older population and are therefore not validated in this population Low values of maximum quantity that maximized sensitivity and specificity among individuals aged 65 and older support a lower risk drinking threshold for individuals in this age group (Dawson et al., 2010)

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consumed on any day Two Screening Questions (Cyr and Wartman, 1988): 'Have you ever had a drinking problem?' and 'When was your last drink?'	physicians due to ease of use	
Laboratory tests		
Main Features	Advantages	Disadvantages
Blood testing e.g. Mean Cell Volume (MCV), gamma-glutamyltransferase levels (Gamma GT) and aspartate aminotransferase (AST)	May show damage relating to alcohol use in older adults at lower levels of consumption therefore being a more sensitive test in the older adults (Caputo et al., 2012) Objective measurement Useful as corroborative evidence as high sensitivity but low specificity (Mears and Spice, 1993)	Di Bari et al. (2002) found CAGE and MCV/Gamma GT to be positive in only a minority of at-risk drinkers. There was a very low concordance of both tests being positive. Participants over 75 years drank less but had similar prevalence of CAGE and MCV/Gamma GT positive. Invasive test, but only minimally Low sensitivity and specificity (Mangion et al., 1992)
CAGE Questionnaire		
Main Features	Advantages	Disadvantages
<u>C</u> utting down, <u>A</u> nnoyance by criticism, <u>G</u> uilty feelings and	Widely used (Culbertson, 2006). Easy to remember and administer and easy to score	Not developed specifically for older adults Focuses on dependence and not harmful use

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Eye openers (Ewing, 1984) Positive result is indicated by two positive responses. Developed for use in primary care setting.	A score of 1 or more had sensitivity of 86% and specificity of 78% for detecting alcohol issues in medical outpatients >60 years (Buchsbaum et al., 1992) In older adults aged 70–75 a cut-off score of 2 or more was associated with sensitivity of 29% and specificity of 37%, this improves to sensitivity of 70% and specificity of 92% with cut-off score of 1 or more (Rozzini and Trabucchi, 1993) CAGE is valuable for screening for dependence in the older adults using cut-off of 1 or more (Berks and McCormick, 2008) May have a better role as corroborative evidence alongside other methods as high sensitivity but low specificity (Mears and Spice, 1993) A study comparing CAGE with MAST showed both to have low sensitivities in older adults at conventional cut-off points but CAGE was more effective overall (Jones et al., 1993)	Looks at lifetime use and not current habits so if used should be combined with assessment of current consumption Low sensitivity (Mangion et al., 1992) Identified fewer than half of the heavy drinkers in a group of over 60-year olds, using cut-off of 1 may increase sensitivity. (Adams et al., 1996) Only a small number of at-risk drinkers aged over 65 scored 1 or more on CAGE. (Di Bari et al., 2002) Less than half of those screening positive on either the SMAST-G or the CAGE screened positive on both measures suggesting they may be capturing different aspects of alcohol misuse. Using a combination of tools may be beneficial. (Moore et al., 2002b) May be of useful limitedness as older adults may not be aware current level of intake is hazardous or harmful and as such may never have felt guilty or tried to cut down (Culbertson, 2006)

Alcohol Use Disorders Identification Test (AUDIT)		
Main Features	Advantages	Disadvantages

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Not evaluated for use in older adults however has been cross culturally developed by World Health Organization in the 1980s (Saunders et al., 1993) Administered as interview or completed by the patient It contains ten questions, the first three of which cover alcohol consumption (amount and frequency) Responses are scored from 0 to 4 giving a maximum possible score of 40. 8 used as cut-off score.	Its strength lies in its ability to identify those who have problems with alcohol but may not yet be dependent (Berks and McCormick, 2008) Takes only a few minutes to complete Provides information on current quantity and frequency of drinking (Culberson, 2006) In over 65s, cut-off score of 8 or more had sensitivity of 0.48, this improved to >0.85 with cut-off of 5 or more (Aalto et al., 2011) Cut-off of 8 had sensitivity of 0.7 and specificity of 0.95 in >65s (Gomez et al., 2006) A study in older male Koreans found AUDIT had greater diagnostic power than SMAST-G and CAGE (Ryou et al., 2012) Anaesthetists identified 7% of alcohol use disorders using clinical assessments versus 18% for	Not developed specifically for older adults and has performed poorly in older adults in some studies and the lack of yes/no answers may complicate scoring (Culberson, 2006) In older male hospital patients, a cut-off of 8 or more had sensitivity of 33% and specificity of 91%. Cut-off of 4 or more improved sensitivity only to 59% and specificity decreased to 41%. The AUDIT was outperformed by MAST-G and CAGE (Morton et al., 1996) Asking about meeting responsibilities may not be useful in an older population and items concerning the amount of alcohol consumed again may not be appropriate in older adults due to harm at lower levels of consumption.

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	AUDIT (Spies et al., 2008)	
AUDIT-C		
Main Features	Advantages	Disadvantages
The AUDIT - C (consumption) is a shortened version of the AUDIT, using the first three questions only, i.e. how often the person drinks, how many drinks on a typical day, and how often the person drinks six or more drinks on one occasion	AUDIT-C was shown to have nearly identical sensitivity as the full audit in the general primary care population (Bradley et al., 2007) Shorter and quicker to administer. Optimal cut-off of AUDIT-C score was 4 in those over 65 years of age (Aalto et al., 2011)	Not developed specifically for the older population.
Michigan Alcoholism Screening Test - Geriatric Version (MAST-G) and shortened version (SMAST-G)		
Main Features	Advantages	Disadvantages
MAST-G contains 24 yes/no questions and SMAST-G ten yes/no questions. Items on the test cover the physical signs of excessive drinking, the connection between drinking and emotional states, problems controlling level of consumption, and the reactions of others to the person's drinking. It can be self-administered or completed by the	The original MAST-G instrument from which the SMAST-G was derived has a sensitivity of 93.9%, specificity of 78.1% when measured against DSM-III-R criteria (Blow et al., 1992). SMAST-G may be useful due to its brief nature.	Takes 10 minutes to administer, which might limit its usefulness in clinical practice and does not differentiate current from past drinking or change in consumption over time and does not include any quantity-frequency questions. Professionals may be unaware of its existence (Naegle, 2008).

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physician. It focuses more on harmful drinking than alcohol dependence. It may be more sensitive to picking up problems in older adults as it puts less reliance on the effects of alcohol misuse on routine and commitments and more emphasis on the effects of alcohol misuse on family relationships, the involvement of losses and bereavement in the development of alcohol use disorders, the physical effects of drinking, and the interplay between psychological difficulties and development of AUDs (Naegle, 2008).	Scoring is simple (Naegle, 2008). Blow et al. (1998) found SMAST-G to have sensitivity of 85% and specificity of 97% compared with DSM-III-R diagnosis of alcohol abuse or dependence. In male veterans aged 65 or over scores of 5 or more were associated with 70% sensitivity and 81% specificity using DSM-III-R as gold standard. (Morton et al., 1996). A study investigating the effectiveness of MAST-G, SMAST-G and two-item mini MAST-G in identifying hazardous drinking among older adults with CVA, aged over 50 years found all the measures to be useful with comparable sensitivity. (Johnson-Greene et al., 2009). The SMAST-G correctly identified 52% to 85% of older adults with alcohol problems	Moore et al. (2002b) found that less than half of those screening positive on either the SMAST-G or the CAGE screened positive on both measures suggesting these screening tools may be capturing different aspects of alcohol misuse. Those screening positive on SMAST-G drank less than those positive on the CAGE and SMAST-G may be better at identifying those drinkers. They recommend using a combination of screening measures to identify higher numbers of older persons with AUDs. A study comparing CAGE with MAST (Jones et al., 1993) showed both to have low sensitivities in older adults at conventional cut-off points but they report the CAGE was significantly more effective than the MAST in discriminating between older medical outpatients with and without alcohol abuse or dependence. They did not include the geriatric version of MAST.

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	and 93% to 97% of older adults who do not have alcohol problems (Moore, 2001, Blow et al., 1998). Hirata et al. (2001) investigated use of MAST (non-geriatric version) in geriatric outpatients in Brazil compared with DSM-III criteria and found sensitivity of 91% and specificity 84%.	
Alcohol-Related Problems Survey (ARPS) and Short ARPS (sARPS) and Computerized-ARPS (cARPS)		
Main Features	Advantages	Disadvantages
Developed by Fink et al., 2002a in primary care clinics to specifically screen older adults over 65. Self-administered questionnaire of 60 items. Includes items on presence of medical and psychiatric conditions, symptoms of disease, smoking behaviour, medication use, physical function and health status, quantity and frequency of alcohol use, episodic heavy drinking, symptoms of alcohol abuse and dependence, driving after drinking, and gender. It moves away from focus on dependence and abuse to identify a much larger	Found to be more sensitive than the AUDIT and the SMAST-G at identifying those at risk. (Moore et al., 2002a) Validated against CAGE, SMAST, and AUDIT and correctly identified those who screen positively on these tests 91%, 75%, and 100% of the time respectively. Majority of ARPS identified hazardous or harmful drinkers did not screen positive on CAGE, SMAST, or AUDIT.	Sixty items to complete and uses scoring rules system, which may limit its usefulness in busy clinical settings. (Culbertson, 2006). Takes 16 minutes on average to complete.

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population who are at risk due to comorbidities, medication use, and functional status. Also identifies dependent drinking.	These drinkers had medical conditions or used medications that placed them at risk none of which was addressed by the other three screens (Fink et al., 2002b)	
ASSIST (Alcohol, Smoking and Substance Involvement Screening Test)		
Main Features	Advantages	Disadvantages
Developed by World Health Organization. Aims to screen for problematic or risky substance use. Eight questions covering tobacco, alcohol, cannabis, cocaine, amphetamines type stimulants, inhalants, sedatives, hallucinogens, opiates, and other drugs. (Khan et al., 2012)	Khan et al. (2012) demonstrated significant correlations with other measures of alcohol use disorders using ASSIST in French geriatric outpatients (over 65 years). Screens for a wide range of substance use disorders and detects substance use, abuse, and dependence. User friendly and quick to administer.	Covers other substances in addition to alcohol and so may be less acceptable to an older population.

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For example, if time is limited, the AUDIT-C may be used to collect brief, reliable information about quantity and frequency of alcohol use (it can also be used to calculate risk thresholds), while the SMAST-G (tailored for older people) can collect brief information about harms the patient may

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be experiencing as a result of alcohol use, such as falls, interactions with medication, and memory problems like forgetting.

Taking a substance misuse history in an older person

The approach to assessment is key to obtaining a comprehensive overview of substance use and misuse, with a view to formulating a risk assessment and management plan (Rao et al., 2015).

General principles

Adopting a non-judgmental and non-ageist approach is essential, as is maintaining respect for dignity and autonomy. An interpreter may be required if English is not the patient's first language. The pacing of the interview needs to take into consideration factors such as seating comfort, sensory impairment, clouding of consciousness, level of comprehension, cognitive impairment, and privacy. Underreporting of substance use may occur because of denial, stigma, lack of awareness, or memory impairment.

Additional information from other sources can include relatives, friends, and informal carers. Other information may also come from GP consultations, hospital discharge summaries, home carer reports, day centre reports, reports from housing officers/wardens of supported housing, criminal justice agencies, and results from previous investigations (including cognitive testing and neuroimaging).

The assessment will lead to a formulation and management plan that takes into account possible medical comorbidity, functional abilities, the influence of loss events on mood state, cognitive state (including the influence of substances and physical disorders), and availability of social support. Table 46.2 outlines a systematic approach to assessment of possible substance misuse problems.

Table 46.2 Systematic approach to assessment.

Area of Questioning	Questions to Ask
Substance use (cover alcohol and each substance individually)	• Age of initiation: first tried each substance • Age of onset of weekend use; weekly use; daily use • Pattern of use during each day, i.e. quantity/weight, frequency • (If alcohol) Drink type. If drinking at home: glass size, typical 'pour'. • Route of use and access to substances • Evidence of physical dependence

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	• Current use over previous day/week • Number of days of abstinence (reasons for this) • Periods of abstinence and triggers to relapse • Episodes of intoxication, withdrawal or overdose
Treatment episodes for substance misuse	• Dates and length of contact with service • Outcome of intervention
Family history	Alcohol and substance misuse in parents, siblings, grandparents, other relatives, spouse/partner, children
Family psychiatric history	Cover suicide, self-harm, depression, anxiety, psychotic illness, alcohol-related brain damage/dementia
Personal history	• Educational attainment • Psychosexual history, including nature and quality of relationships (e.g. domestic abuse, carer alcohol/substance misuse) • Occupational history
Social history	• Current living arrangements and living conditions • Formal and informal carers and carer burden • Marital biography • Social network • Activities of daily living/self-neglect • Housing • Driving • Finances/benefits/debt • Any safeguarding matters • A typical day

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Lifestyle issues	• General physical state • Sleep • Diet • Oral health
Medical history	• Ongoing medical disorders • Mobility, hearing and eyesight • Medication (prescribed and over the counter) • Hepatic, cardiovascular, respiratory, gastro-intestinal, neurological complications. • Blood borne viruses (hepatitis B, C and HIV) • Falls, pain, constipation, sensory impairment • Admission to hospital, dates, problems, treatment, length of admission and outcome • GP contact and health checks
Psychiatric history	• Current mental health problems or disorders • Treatment by GP with psychoactive drugs • Contact with secondary care psychiatric services • Any mental health act assessments
Forensic history	• Cautions, charges, convictions • Types of offences (e.g. acquisitive, offences against the person) • Imprisonment at any time • Ongoing contact with forensic services

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Social background/ Personality	• Ethnicity and cultural background • Religious and spiritual beliefs • Coping styles/resilience
Biological and psychological measures	• Biochemistry: alcohol levels, drug screens, liver function tests • Haematology • Virology • Brain MRI • Liver ultrasound • Endoscopy • Cognitive assessment
Further information	• Carers, family, friends • Other service providers
Perspective of patient	• Awareness of problems • Motivation for change - strengths, barriers, support

Multiple assessments are often required to build up a clinical picture, including the need for vigilance around safeguarding. Alcohol misuse may coexist with elder abuse. Alcohol abuse may be present in both the abuser and the victim of the abuse (Choi and Mayer, 2000). Elder abuse can present itself in ways that can be mistaken for alcohol problems; for example, bruising, withdrawal, depression, and malnourishment (Wadd and Galvani, 2014).

Clinical diagnosis and problems with using current systems

ICD-10 (World Health Organization, 1992) divides substance misuse into harmful use and dependence. Harmful use is defined as a pattern of psychoactive substance use that causes damage to either physical or mental health. Older people may still have dependence, but ICD-10 criteria may not be a suitable diagnostic tool for use in this age group. Some limitations of the ICD-10 criteria are detailed in Table 46.3.

Table 46.3 Limitations of ICD-10 diagnostic criteria for substance dependence syndrome in older people.

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Three or More of the Following have been Present Over Previous 12 months	Limitations in application of criteria to older people
A strong desire or sense of compulsion to take the substance	Older people may attribute desire to longstanding habit as opposed to compulsion
Difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use	Cognitive impairment may affect self-monitoring Fewer social and family pressures to change substance misuse behaviour
Evidence of withdrawal state through either • Physiological substance specific withdrawal syndrome on reduction or stoppage. when substance use has ceased or been reduced • Use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms	Older people may not develop physiological dependence Withdrawal symptoms may be atypical
Evidence of tolerance, such that increased doses of the psychoactive substance are required to achieve effects originally produced by lower doses	Older people may not develop physiological dependence Tolerance may occur at lower doses than younger people
Progressive neglect of alternative pleasures or interests because of psychoactive substance use	Coexisting physical and mental disorders may have already led to neglect of other interests
Increased amount of time necessary to obtain or take the substance or to recover from its effects	Pre-existing reduced functional ability and social isolation may make comparison problematic
Persisting with substance use despite clear evidence of overly harmful consequences (physical or mental)	Mental capacity may affect awareness of harm

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	Denial or misattribution of harm to physical problems

Source data from International statistical classification of diseases and related health problems, 10th Revision, 2010, World Health Organization.

Older people may already have experienced changes to their independence such that the salience of substance misuse may not be immediately apparent. Cognitive impairment may affect the reliability of self-monitoring. Older people may not experience physiological dependence. They may also attribute a desire for substance use as longstanding behaviour that has been part of a daily routine. Lastly, impairment of mental capacity may render an older person unable to weigh up the risk of harm associated with substance misuse. If these limitations are taken into consideration, it may be necessary to explore changes in drinking behaviour on the basis of collateral information from other sources.

Assessment of comorbidity

Psychiatric disorders

The term comorbidity (or 'dual diagnosis') is used to describe the co-occurrence of one or more mental disorders in the presence of substance misuse. Social problems may also be part of the picture: older people with substance misuse are often very vulnerable, with histories of deprivation, poor educational attainment, and trauma experiences that may even involve violence.

The prevalence of comorbid psychiatric disorders ranges from 21% to 66%, with higher rates seen across in-patient settings for those with more severe mental health problems (Bartels et al., 2006). Older adults with depression are three to four times more likely to have alcohol-related problems than those without (Devanand, 2002), with higher risk of suicide and social/functional impairment (Davis et al., 2008). Those people with dual diagnosis have higher risk of relapse in their mental disorder and hospitalization than those with mental disorder alone (NICE, 2011c).

The inter-relationship between comorbidity and substance use can be complex. Substance use (even one dose) may produce or exacerbate psychiatric or physical symptoms or disorders, and vice versa.

Harmful use may produce psychological and physical symptoms or syndromes. Dependence, intoxication, and withdrawal may all produce psychological and physical symptoms or mental disorders. Comorbid psychiatric disorders are detailed in Table 46.4.

Table 46.4 Comorbid psychiatric disorders accompanying substance misuse

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Psychiatric disorder	Clinical considerations
Depression	• Masked by physical presentations, intoxication, different expression of low mood • Alcohol as a mood depressant • Depression as trigger for alcohol misuse • Accompanying anxiety with 'self-medicating' using alcohol • Increased risk of suicide with alcohol misuse
Psychosis	Acute episode or as part of withdrawal states
Alcohol withdrawal	• Early symptoms • Delirium tremens • Pharmacological treatment • Clinical environment
Alcohol-related brain damage	• Direct and indirect mechanisms • Wernicke's encephalopathy • Korsakoff's syndrome • Alcohol-related dementia

Depression

In older people, low mood may be downplayed, misattributed to cognitive impairment by clinicians (so called 'pseudodementia'), and masked by either physical illness or alcohol intoxication. Rather, they present with feeling 'down in the dumps', 'fed up', or 'lonely'. Older people are more likely to 'somatize' their depression through complaints such as worsening pain or abdominal discomfort. Older people also do not commonly present with the classic depressive symptoms seen in their younger counterparts, such as feeling low and being tearful.

Alcohol itself is also directly associated with depression, which is perpetuated when used to alleviate anxiety or low mood as self-medication. Antidepressant treatment should be used with caution because of potential drug interactions and potentially limited efficacy when someone continues to drink. Stopping drinking may uncover low

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mood and patients should be advised of this and antidepressant treatment may be required.

Similarly, given the restricted lifestyle of some older people, it is difficult to gauge the extent of any loss of interests. Other symptoms such as loss of appetite and sleep disturbance may be shared with both physical health problems and with alcohol misuse, as may loss of energy. However, the diagnosis is made clearer by the presence of pessimism, hopelessness, thoughts of life not being worth living, and suicidal ideation.

The assessment of alcohol misuse is particularly important in older people who are at the highest risk of completed suicide, where alcohol misuse often accompanies the worsening of depressive symptoms and lowers impulse control.

If the person expresses feelings of hopelessness, it is essential to explore suicidal ideation, particularly the severity and frequency of suicidal thoughts, as well as factors driving this ideation and those holding back the person from attempting suicide. This is particularly important when assessing older people who have presented with an act of self-harm. In such cases, the presence of depression with or without alcohol misuse may (under certain circumstances) require the use of legal detention (e.g. the Mental Health Act in England).

Risk factors for suicide cluster together in risk profiles and include male gender, family history of psychiatric disorder, previous attempted suicide, more severe depression, and hopelessness, as well as comorbid anxiety and alcohol misuse (Hawton et al., 2013).

Psychosis

Approximately 40% of people with psychosis develop substance misuse at some point in their lifetime (NICE, 2011b). Substances such as cannabinoids, stimulants, and hallucinogens can induce an acute psychosis while the withdrawal states accompanying alcohol and/or sedatives/hypnotics are also commonly associated with transient psychotic symptoms. Other substances such as nicotine, opioids, stimulants, and cannabis also have distinct withdrawal symptoms presenting with psychotic symptoms (Crome et al., 2015).

Alcohol withdrawal

The possibility of alcohol misuse and the potential for clinical presentations of alcohol withdrawal should be considered in all acutely unwell hospital patients and for those in the community with an established diagnosis of alcohol dependence syndrome.

An alcohol withdrawal syndrome may mask the development of the potentially life-threatening Wernicke's encephalopathy (see Alcohol-related brain damage). Delirium tremens is a severe form of alcohol

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withdrawal that can manifest as a severe mental or nervous system disorder. It is a medical emergency characterized by hallucinations, disorientation, tachycardia, hypertension, fever, agitation, convulsions, and profound sweating and typically sets in following acute reduction or cessation of alcohol. It typically begins 48–96 hours after the last drink and in the absence of complications can last for up to seven days (Mayo-Smith et al., 2004).

Pharmacological treatment is necessary for safe withdrawal from alcohol in patients who are physically dependent. In younger patients, 20mg of chlordiazepoxide four times a day, reduced over seven days, supplemented by additional treatment for symptom suppression, is the usual treatment regimen. For uncomplicated withdrawal in an older patient without significant comorbidity such as liver disease, up to half this dose is indicated, with the dose reduced over ten to 14 days, as withdrawal in older patients may be more severe and prolonged. Other methods of administering benzodiazepines are by ‘front-loading’ (i.e. until light sedation is achieved, at which point no further medication is given) or when ‘symptom-triggered’ (as opposed to a fixed regime). Both these regimens should only be used by suitable trained staff.

Best practice guidance for the use of benzodiazepines in older patients with comorbid physical problems indicates that shorter-acting preparations are preferable (NICE, 2011a). In younger adults, a slow tapering dose of lorazepam starting at 2 mg four times a day is used. Again, up to half this dose is indicated in older patients. Chlormethiazole is not recommended for older patients because of its effect on respiration, cardiovascular complications and the unpredictability of the serum levels achieved (Broadhurst et al., 2003). Carbamazepine has not been evaluated in older populations and is therefore not recommended for the treatment of alcohol withdrawal syndrome.

Pharmacological management needs to be supplemented by regular monitoring of vital signs, adequate hydration, a well-lit environment, and treatment with parenteral thiamine.

Alcohol-related brain damage

There have been major advances in the understanding of the relationship between alcohol consumption and cognitive impairment over the past five years. However, as explored in previous sections of this chapter, research has been hampered by the public focus on the purported health ‘benefits’ from moderate drinking.

Several mechanisms can contribute to the pathogenesis of alcohol-related brain damage (Kim et al., 2012). These include:

- Direct toxicity—frontal and hippocampal damage
- Malnutrition—Wernicke’s encephalopathy/Korsakoff’s syndrome
- Traumatic head injury

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- Cerebrovascular damage (stroke from alcohol related hypertension, traumatic intracerebral haemorrhage, subdural haematoma)
- Metabolite toxicity
- Electrolyte imbalance
- Hepatic encephalopathy/infection
- Inflammatory (e.g. TNF- α)
- Modifying factors (e.g. Apo e allele/elevated homocysteine)

These factors listed may also interact with each other to produce complex clinical presentations. AUDs may also complicate primary dementias, increasing adverse effects and cognitive decline (Withall et al., 2014).

Amnestic syndrome

Amnestic syndromes comprise Wernicke's encephalopathy (WE) and Korsakoff's syndrome (KS). WE is associated with haemorrhage into the thalamus and mammillary bodies. The aetiology of this damage is deficiency of vitamin B₁ (thiamine). WE consists of the combination of ophthalmoplegia, cerebellar dysfunction, and altered mental state, but in practice only 20% of patients present with this full triad. A more common presentation is with apathy, disorientation, and poor attention.

Repeated episodes of WE not treated with parenteral thiamine progress to KS, which is characterized by severe anterograde amnesia and retrograde amnesia extending several years before brain damage. Confabulation occurs as events are invented to fill in absent memories (Kopelman et al., 2009, Thomson et al., 2012). There is preserved short-term memory, as the neuroanatomical impairment results in faulty encoding of information from short-term to long-term memory. Amnestic syndromes are confined to memory and are not classified as dementia.

Alcohol-related dementia

Alcohol-related dementia (ARD) encompasses cognitive impairment that extends beyond memory impairment. Clinical criteria have been developed to improve the diagnosis of probable ARD (Oslin and Cary, 1998). The essential diagnostic features of ARD are evidence of cognitive impairment; significant alcohol use-defined by minimum average of 35 standard drinks (>60 UK units) per week for men and 28 (>48 UK units) for women, for a period of greater than five years; with the period of significant alcohol consumption occurring within three years of clinical onset of cognitive impairment.

A probable diagnosis of ARD is supported by presence of alcohol-related end organ damage; ataxia or peripheral polyneuropathy (not attributable to other non-alcohol-related causes); and neuroimaging evidence of cerebellar atrophy.

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ARD also differs from degenerative dementias in that cognitive damage and ventricular or sulcal dilatation are likely to show partial improvement within the first 60 days of abstinence, particularly in white frontal white matter integrity (Gazdzinski et al., 2010). The presence of marked language impairment (e.g. nominal dysphasia), focal neurological signs or symptoms (except ataxia or peripheral sensory polyneuropathy), or neuroimaging evidence of cortical or subcortical infarction, subdural haematoma, or other focal brain pathology may cast doubt on alcohol having a direct association with the dementia. Although it is equally difficult to gauge with certainty that alcohol has not been contributory if there is a history of heavy consumption.

ARD shows better performance on semantic and verbal memory but poorer performance on visuospatial tasks and frontal tasks compared with Alzheimer's disease (Rao, 2016; Ridley et al., 2013; Zahr et al., 2011). Alcohol-related cerebellar damage may also disrupt frontal processes such as executive function and poor response inhibition (Pitel et al., 2015).

Traditional screening tools for cognitive function (e.g. the Mini Mental State Examination) do not include tests of frontal lobe function, so if a more comprehensive assessment of cognitive function is required, more detailed instruments such as the Addenbrooke's Cognitive Examination (Mioshi et al., 2006) can be used.

There remains scope for further exploration of the association between alcohol misuse and dementia, and there are many unanswered questions including the rate of progression and possible reversibility; the relative roles of thiamine deficiency compared with more direct effects of alcohol toxicity; the interplay with other pathology and traumatic brain injury; and the role of drug treatment in improving cognitive impairment and behavioural problems.

Physical disorders

Systemic effects of substances include gastrointestinal disease (e.g. damage to the liver and pancreas from alcohol misuse); respiratory disorders (e.g. chronic obstructive pulmonary disease (COPD) and lung cancer from tobacco smoke or cannabis and chronic nasal inflammation from crack cocaine); low blood sugar (from misuse of cocaine and alcohol); cardiac disease from alcohol and cocaine misuse, haemorrhagic stroke from alcohol, cannabis, cocaine, amphetamines, phencyclidine (PCP) and lysergic acid diethylamide (LSD); as well as complications from intravenous drug use.

Acute hazards from intravenous injections include damage to veins, infection, and overdose, with such damage representing the most common harm from misuse of cocaine. Bacterial endocarditis and Hepatitis C can also arise because of injecting drugs.

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Physiological changes associated with age, sensory deficits, postural imbalance, chronic health problems, substance misuse, and environmental hazards have all been identified as risk factors for falls. Loss of balance, coordination, judgment, risk taking, autonomic neuropathy, peripheral neuropathy, cardiac disease, osteoporosis, and myopathy may all act synergistically to make a fall more likely. There is an increased prevalence of falls among elderly individuals with substance misuse and therefore the possibility of substance misuse should always be considered in the differential diagnosis of falls. Weight loss and poor self-care may also be manifestations of alcohol misuse. Areas of physical examination to be covered in older people with substance misuse are detailed in Table 46.5.

Table 46.5 Physical examination in substance misuse.	
Area of physical examination	Clinical considerations
Oral	Gum disease and dental caries from poor nutrition secondary to substance misuse
Skin and nails	• Injury • Skin breakdown from pressure areas • Damage from incontinence • Vasculitis, purpura, scleroderma, and Raynaud's syndrome from cocaine misuse • Tar staining of skin from tobacco • Palmar erythema, spider naevi, psoriasis, skin carcinoma, and porphyria cutanea tarda from alcohol misuse • Nail fold infarcts, splinter haemorrhages, Osler's nodes in the pulps of the digits, Janeway lesions (tender nodules in the palms or soles) from intravenous drug misuse
Abdomen	• Hepatomegaly with macronodular surface from alcohol misuse • Caput medusae and ascites from portal hypertension secondary to alcohol misuse
Cardiovascular	• Hypertension from alcohol misuse, smoking, and stimulants

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	• Heart failure with ischaemic heart disease from smoking or stimulants • Ischaemic heart disease, vascular disease, heart failure, and stroke • Cardiomegaly from alcohol misuse • Valvular disease, thrombophlebitis, deep vein thrombosis, and subacute bacterial endocarditis from intravenous drug misuse
Respiratory	• COPD from tobacco and cannabis misuse • 'Crack lung' from cocaine misuse • Lung cancer from tobacco smoking
Neurological	Cerebellar syndrome and peripheral neuropathy seen from alcohol dependence

Drug interactions with and between substances

Alcohol, nicotine, opioids, benzodiazepines, and the Z drugs form the majority of substances taken by older people. However, there is now increasing use of pregabalin in the treatment of anxiety. Although there may be the potential for misuse, this is commonly at higher doses and with people who have a history of substance misuse (Schifano et al., 2011). Its potential for misuse in the treatment of older people with anxiety remains to be seen.

Alcohol, nicotine, opioids, benzodiazepines, and Z drugs can interact pharmacodynamically by augmenting adverse side-effects at a receptor level and/or by interaction at the stage of drug absorption, distribution, metabolism, or excretion through pharmacokinetic mechanisms. This latter interaction results in changes to the levels of the substance or other drugs in the body through increased or decreased drug metabolism. At high levels, alcohol, benzodiazepines, and opioid all have a sedative action. If taken in combination, there is an increased risk of falls and respiratory depression.

Alcohol

Alcohol has the potential for several adverse interactions with both prescription and non-prescription drugs. Women are at higher risk of drug interactions with alcohol than men (Baxter and Preston, 2010). Women tend to have a higher fat-to-water ratio and therefore a higher blood alcohol concentration than men for a given amount of alcohol consumed. Food and milk decrease the rate of alcohol absorption.

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Polypharmacy is also common in older people, with 40% taking five or more prescription drugs (Wilson et al., 2007).

The most common drugs implicated are benzodiazepines and amitriptyline (Gallagher and O'Mahony, 2008), which potentiate the sedative effect and increase the risks of falls. There is also a potential interaction between opioid-containing drugs (morphine and codeine) and alcohol. Alcohol is also associated with rapid release of morphine from extended-release preparations. Important interactions between alcohol and other drugs are detailed in Table 46.6.

Table 46.6 Drug interactions with alcohol.		
Drug	Interaction	Outcome
Over-the-counter drugs	Topical Pharmacokinetic	Aspirin ↑ risk of bleeding into the gut Heavy drinking ↑ risk of liver damage from paracetamol
Some antibiotics	Pharmacokinetic (Disulfiram like reaction)	Flushing, headache, palpitations, vomiting.
Nicotine patches	Pharmacodynamic	Tachycardia
Psychotropic drugs (antidepressants, antipsychotics, anxiolytics)	Pharmacodynamic	↑ drowsiness
Opioid analgesics	Pharmacodynamic	↑ risk of falls/ respiratory depression
Sedating antihistamines	Pharmacodynamic	↑ risk of drowsiness
Anti-hypertensive drugs	Pharmacodynamic	↑ risk of low blood pressure/falls
Warfarin	Pharmacokinetic	Acute alcohol intake: ↑ levels Chronic alcohol intake: ↓ levels

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Anti-emetics	Pharmacokinetic	Metoclopramide ↑ Alcohol levels
Anti-epilepsy drugs and mood stabilizers	Pharmacokinetic	Carbamazepine levels ↓ by heavy drinking; Blood alcohol levels ↑ by meprobamate

Opioids

The two terms, opiates and opioids, have been used interchangeably, but it is now more common to refer to both as opioids. Drug interactions with opioids are shown in Table 46.7. Morphine, naloxone, and naltrexone are relatively less affected by pharmacokinetic interactions with other drugs.

Table 46.7 Drug interactions with opioids.

Drug/food	Interaction	Outcome
Ciprofloxacin Clarithromycin Erythromycin Itraconazole Ketoconazole Ritonavir Diltiazem Grapefruit juice Nefazodone	Pharmacokinetic	↑ effect of buprenorphine, methadone, and loperamide
Carbamazepine Phenytoin Phenobarbitone Rifampicin St John's wort	Pharmacokinetic	↓ effect of buprenorphine, methadone, and loperamide
Fluoxetine Paroxetine Metoclopramide Quinidine	Pharmacokinetic	↑ effect of oxycodone, codeine, dihydrocodeine, and tramadol
Amiodarone Propranolol Ciprofloxacin Rifampicin Duloxetine Fluvoxamine	Pharmacokinetic	↑ effect of pentazocine

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Olanzapine Clozapine Caffeine		

Nicotine

On its own, nicotine alone has few interactions with other drugs. Its metabolism is inhibited by ketoconazole, isoniazid, and grape juice, thereby increasing blood levels. Phenobarbitone and rifampicin are associated with enzyme induction and reduced blood levels. The most common exposure to nicotine is through tobacco smoke, which contains polycyclic aromatic hydrocarbons that affect the same enzyme pathway affected by pentazocine metabolism. Carbamazepine levels are decreased by chronic smoking.

Drugs for anxiety and insomnia

Benzodiazepines, buspirone, zopiclone, and the benzodiazepine antagonist flumazenil are metabolized by the same pathway as buprenorphine, methadone and loperamide and are therefore induced and inhibited by the same drugs as these opioids.

Treatment of substance misuse in older people

There are surprisingly few in-depth reviews of treatment options and their effectiveness for older people. This section reviews areas of consideration for treatment for older people. It should be noted that most treatment studies focus on reduction of alcohol and prescription medication, and less is known about treatment for abuse of other substances in this group.

Establishing the patient's goal

From the beginning, there needs to be a sense of what the patient expects or wants to achieve during treatment. Complete abstinence is one approach. However, some patients may still want to continue use but at a lower level. For some people 'controlled drinking' or reduced use of other substances may be a preferred alternative to abstinence. However, it should be considered whether even this 'controlled' level is low enough to be safe for the patient.

Barriers to entering or re-entering treatment

Some of the barriers to detecting substance misuse are discussed earlier in this chapter. Similar individual, societal, and professional barriers also influence entering or re-entering treatment for substance misuse. Some patients, particularly if LO, may be entering treatment for the first time, while others may have been through one or many treatments in the past. Kuerbis and Sacco (2013) describe three inter-related barriers to treatment entry for older patients: the societal myth that older people do not abuse substances; the belief that people who have experienced

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problems with substances earlier on in their life cannot get better; and that entering pre-existing treatment groups with younger adults can be daunting due to stigma or shame.

A careful exploration of concerns at this stage may prevent the likelihood of drop out or disengagement in treatment in the future. If the person has been abstinent for a number of years but has now relapsed, this can be disheartening and may contribute to depression or hopelessness about treatment success. Reasons for drop out or disengagement in the past should be collected, as these factors are likely to influence engagement with subsequent treatment.

To motivate the patient, communicate that there is good evidence to show that appropriate treatment can be particularly effective for their age group. As stated by the Royal College of Psychiatrists (2011, p. 8): 'older people can and do benefit from treatment, and in some cases have better benefits than younger people'. Satre and colleagues (2004) found that 20% of older people with alcohol dependence who went through treatment remained abstinent after four years. They also found that women were more likely to remain abstinent compared to men. Thus, it should be reiterated, older people with alcohol and substance use disorders can and do recover and experience an improved quality of life, providing the treatment they receive is tailored to their needs (Han et al., 2009).

Factors influencing effectiveness of treatment

Kuerbis and Sacco (2013) reviewed the factors that influenced the effectiveness of treatment in older people. It should be noted most studies in their review were from the US, and many were with veterans, but nonetheless, the findings are relevant to planning substance misuse treatment for an older person.

- Older people who have sought treatment do better than those who have not (e.g. those who have screened positively for high-risk substance use, and received brief advice about drinking from a doctor)
- Outcomes of treatment are mixed for those who receive brief advice alone.
- The more the person has been exposed to, or attended, treatment, the better the success rate.
- Patients with LO may have a higher motivation for treatment while those with EO are more likely to drop out of treatment (Schonfeld and Dupree, 1991).
- If a person engages with a full course of treatment, outcomes are positive.
- Age-specific treatments are more effective for an older group (this could be due to lower drop-out rate). Examples of age-specific adjustments that can be made include: location of treatment programme (accessibility), materials used (to account for physical or

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cognitive functioning problems), slower pace of treatment, and group treatment with others of a similar age (due to stigma).

- Providing education, harm reduction, or brief information about risks of heavy drinking using brief intervention have more benefits than not providing it at all.

The Royal College of Psychiatrists (2015) highlight other factors influencing the effectiveness of treatment in this group. These include:

- Taking into account the complex needs of the patient, such as loneliness or physical disability, increases treatment effectiveness.
- Engaging other services, such as health and welfare agencies, helps provide the patient with additional support to promote recovery.
- Providing an older person with practical advice as well as specific treatment. For example, helping an older person to fill their time after reducing or stopping substance use reduces relapse.
- Engaging and supporting other important people in the older person's life can be helpful, e.g. carers.

Specific treatment approaches

Cognitive behavioural therapy (CBT)

CBT may be a particularly appropriate strategy if the person is using substances to cope with specific thoughts, emotions or physical states. The focus of CBT in this case may be on identifying high-risk situations, working on coping strategies and problem-solving skills, and identifying emotions and stressors as triggers to substance use. CBT can be just as effective for older adults as for younger people (for example, Dupree et al., 1984), though there is a surprising lack of recent research in this area.

Although CBT is an appropriate strategy to improve an older person's ability to cope with stressful life events, consideration should be given to how it is delivered. For example, CBT relies on the use of self-help materials such as workbooks to complete at home, thus treatment materials may need to be adapted for use with older people. For CBT to be effective, the person needs to have insight into their thoughts, emotions, and behaviours. Such an approach may not be suitable for those with cognitive impairment. Finally, the optimal intensity of CBT for best outcomes is unknown, and it is often combined with other approaches, such as motivational interviewing (MI). An example of a successful treatment package will be reviewed later in this section.

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Motivational interviewing (MI) or motivational enhancement therapy (MET)

Motivational interviewing is described as ‘a skilful clinical style for eliciting from patients their own motivation for making changes in the interest of their health’ (Rollnick et al., 2008, p.24).

The success of MI can be attributed to the therapist’s ability to develop rapport with the patient by expressing empathy, exploring resistance to change, reflecting back to the patient a discrepancy between current behaviour and future goals, and developing a person’s sense of control and confidence. All of these goals can be therapeutic for an older group. The rebuilding of sense of control or self-efficacy can help with comorbid symptoms such as feelings of low self-esteem and worthlessness, and the development of a relationship with the practitioner can help with loneliness or social isolation. A non-judgmental approach may reduce feelings of shame.

There is evidence that MI can change health behaviour in older adults, though no best practice review exists. As with CBT, MI is often delivered as part of a treatment package so it is difficult to isolate the mechanism for change.

As with other interventions, for MI to be effective with this age group it needs to be delivered at a slower pace, to use repetition to aid memory, and to be flexible enough to adapt to the needs of the individual e.g. those with cognitive impairment (Serdarevic and Lemke, 2013).

Treatments involving the family

Support from family members, or specific family therapy approaches may help an older person to strengthen their social network. Substance misuse can cause relationship problems with spouse and other family members. The person who abuses substances may find themselves increasingly isolated from their family members. Such isolation can worsen problems. On assessment, it is important to consider whether the patient would like family members to be involved in their treatment. Groups such as Al-Anon can be helpful for those who are directly affected by the person’s substance misuse (for example, a person’s spouse, child, or carer).

Alcoholics Anonymous (AA), Narcotics Anonymous (NA), or other twelve-step facilitation (TSF) approaches

Alcoholics Anonymous (AA) or Narcotics Anonymous (NA), based on the twelve-step approach, are popular peer support groups for reduction of alcohol or substance use. There is no specific evidence for AA for an older group; however, Moos and colleagues (2010) integrated AA into a treatment package with other approaches and found that only AA reduced high-risk alcohol consumption and problems at follow-up. AA may however be less effective in complex cases with medical comorbidity or

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involving polysubstance (e.g. alcohol and prescription medication) use (Donovan et al., 2013).

Furthermore, the twelve-step approach is based on the conception of substance dependence as a spiritual and medical disease (Nowinski, 1992). Such an approach can be very helpful for some, but may not be suitable for people who do not accept this philosophy. We have already seen that mixed age groups are less favourable for older people, and accessibility or the pace of the group can be a barrier to treatment or a catalyst for drop out. However, AA or NA groups can help people strengthen positive peer networks, and provide mutual support. Group treatments increase social contact, and can be particularly beneficial for those who live alone.

Other approaches

Those with LO who have a clear trigger to substance misuse may particularly benefit from compatible treatment approaches such as bereavement counselling. For those who are lonely or socially isolated, evidence shows that interventions addressing social cognitions are effective. For example, discussion groups to talk about loneliness and develop relationship skills were particularly effective for women (Masi et al., 2011).

Examples of successful treatment programmes in different settings

Treatment effectiveness appears to be influenced by the setting where the treatment takes place as well as by the motivation of the participants. Here we list published examples of effective treatment packages offered in three different settings.

Brief intervention

In the Florida BRITE Project (USA) (Schonfeld et al., 2010) brief intervention was provided after community screening using the SMAST-G (to measure alcohol problems). Abuse of prescription medication was also explored in this study (pain medication, anxiolytics, sleeping medication, and 'medication for loneliness or sadness'). Symptoms of depression and suicide risk was measured by the Short Geriatric Depression Scale (SGDS, Sheikh and Yesavage, 1986). Age-related adjustments were made for the individual in this intervention, for example, home visits if the person had poor mobility. MI was used to increase motivation for treatment, and 16 sessions of CBT were provided.

Results showed an overall significant reduction in SMAST-G scores after treatment, with only 19% (compared to 80%) of people scoring positively for alcohol problems at discharge and follow-up. The treatment programme also reduced prescription medication misuse in 32% of people who were flagged as having problems at baseline. Overall, treatment reduced symptoms of depression.

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In this study, patients had a lot of contact with intervention staff, and this in itself may have influenced the outcome. This study indicates that intensity of treatment and multimodal methods tailored to the individual were important. It also demonstrated how such treatment may target other risk factors such as depression, loneliness and social isolation.

Outpatient treatment

The Gerontology Alcohol Project (GAP; USA) pilot programme by Dupree and colleagues (1984) was specifically for people with LO alcohol abusers aged 55 or over. The treatment package included CBT, self-management and education delivered in a group of similarly aged older adults. Results showed that 74% of people who stayed in treatment achieved their goal of abstinence or controlled use, but half of the original group of participants dropped out at the start.

This study demonstrates the importance of identifying barriers to treatment at the outset. Those who stay the full course generally have good outcomes.

Inpatient treatment

Based in the US, this substance abuse treatment (SAT) study by Slaymaker and Owen (2008) followed 67 in-patients who were alcohol dependent. Treatment included individual and group therapy and community activities. Approaches used included CBT, MET, and 12-step groups. Special groups were held to explore challenges of later life including grief, life course transitions, and how to spend leisure time.

Results showed that 71% of patients were abstinent at 6-month follow up, and 60% abstinent at 12 months. Improvements were measured by the Addiction Severity Index (ASI) which was a useful assessment tool for this purpose. Treatment adaptations included: better accessibility for those with poor mobility, slower pace and modifications for sensory or cognitive impairments. This study showed that tailored group treatment addressing triggers to substance misuse are helpful, and focusing on these triggers may result in sustained change.

Efficacy of brief intervention

Brief interventions can be effective in reducing alcohol and substance misuse if delivered appropriately. The Royal College of Psychiatrists (2015, p. 13) suggest three simple ways to deliver brief advice:

1. a sentence or two of feedback based on a person's AUDIT score
2. a sentence or two of feedback, plus an information leaflet
3. five minutes of advice based on FRAMES structure.

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The FRAMES model provides an effective structure for brief intervention (Blow and Barry (2012, p. 317):

- **Feedback** is given to the individual about risk (of alcohol and substance misuse).
- **Responsibility** for change is placed with the individual receiving the intervention.
- **Advice** for changing behaviour is given by the clinician.
- **Menu** of alternative options for change is offered.
- **Empathic** and motivational style is used by the intervener.
- **Self-efficacy** or empowerment is promoted.

Personalized feedback about a person's substance use or misuse is superior to general health information in reducing binge episodes, and agreeing on a 'contract' or shared goal can be powerful for brief intervention (Fleming et al., 1999). However, as we have already seen, for people with complex needs, a brief approach is not likely to be enough for significant sustained change.

Reducing relapse

For the purposes of clear terminology, lapse refers to a single occasion 'slip', while relapse refers to return to alcohol or substance abuse (Barrick and Connors, 2002). If a person is currently trying to cut down or stop using substances completely, treatment discussion may involve planning for risky situations where they may lapse, and identifying what factors can trigger a relapse.

Marlatt and Gordon (1978) found that risky situations for older people tend to involve negative emotional states, where alcohol or substances may be used to relieve negative emotion. A step towards productive treatment planning in an older group is to identify high-risk situations, and to discuss motivation to learn new ways to cope with these situations. The treatment approaches previously discussed can directly target these factors.

Pharmacological treatment

There is a lack of evidence for the pharmacological treatment of substance misuse in older people, with this age group mostly excluded from clinical trials. There is no direct evidence on methadone maintenance treatment in older people or for drugs such as naltrexone and buprenorphine. There is a similar absence of evidence for the pharmacological treatment of abstinence from alcohol in older people using drugs such as disulfiram or acamprosate (NICE, 2011a). A community study involving people aged 65–74 on nicotine replacement therapy (NRT) found 29% of participants self-reported smoking cessation at six months (Orleans et al., 1994). There is currently no evidence to

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guide clinicians in the use of bupropion and varenicline for smoking cessation in older people.

Driving and substance misuse

In the UK, between 2015 and 2016, 6.8% of people aged 50 or over reported that they had driven while thinking they were over the legal alcohol limit at least once in the last 12 months (Department for Transport, 2016). The proportion of drug driving (driving while thinking they are under the influence of illegal drugs) is lower, with just 0.3% of people aged 50 or over reporting this (compared to 1.9% of people aged 20–24).

At a population level, and compared to a younger group, alcohol-related accidents in older people are still relatively low. For example, in the UK in 2014 there were 290 drink drive accidents involving drivers aged 60 or over, compared to 1,020 in those aged 20–24 (Department for Transport, 2014).

However, the number of older drivers is likely to increase. A report by the Automobile Association estimated that by 2030 more than 90% of men over 70 will be on the road, with 21 million older people driving by 2035 (Automobile Association, 2017).

People who misuse substances who still have a car and a current driving licence should be considered 'high risk'. Driving while intoxicated is dangerous and illegal, and if a person continues to engage in this behaviour, they risk being caught (e.g. legal problems), hurting themselves, or harming others. These complications can interfere with any positive progress they are making in recovery (Royal College of Psychiatrists, 2015).

The following issues should be explored with older patients who present with substance misuse and still drive:

- How often do they drive, and what proportion of these occasions do they drink (or use other substances) and drive?
- At what time of day do they usually drive? It should also be emphasized that a person may still be over the legal limit the morning after heavy drinking. However, fewer retirees may be on the road in the morning as they do not have to attend work. Some people may be aware of when roads are likely to be busy, and avoid driving during this time.
- Do they take other medications that also affect driving ability? Awareness of these risks should be explored.
- Are they aware of the drink drive limit? Can they explain the limit in number of drinks (or drink type)?

- Have they ever been stopped or convicted for drink driving? Those who engaged in this behaviour for a number of years and have never been 'caught' may be more likely to keep doing it (Sykes et al., 2010).
- How do they judge whether they are fit to drive? A person may rely on 'how they feel' rather than number of drinks consumed before getting in the car.

In some cases, a person may need to stop driving, for example, if they lose their license. This may cause profound difficulties, e.g. if they live in a remote rural area, or present a barrier to treatment if they need a car to be able to attend treatment sessions or AA meetings. In these circumstances, a sensitive but realistic discussion of transport options is required.

Developments in policy and practice

The first UK report on substance misuse in older people, *Our Invisible Addicts* (Royal College of Psychiatrists, 2011), made the following recommendations:

- At a policy level, to develop clinical guidelines through care pathways.
- At an educational level, to develop training packages for health professionals.
- At a public health level, to developing a consensus on drinking limits.

The first two recommendations have been taken forward and are discussed in the next section. The third has been subject to increased scrutiny, given the complexity surrounding the lack of a specific 'dose-response' effect from alcohol on health outcomes (Crome et al., 2012). The new guidelines on low-risk drinking are discussed earlier in the chapter.

There has since publication of a good practice commissioning guidance from the National Institute for Health and Care Excellence (NICE, 2011a). This highlighted the need for lower thresholds for high-risk groups (including older people) when commissioning in-patient and residential medically assisted alcohol withdrawal services.

It also included examples of good practice when commissioning for older people, such as community-based interventions, addressing complex needs, equality of access to services, and patient experience. An Information Guide for health and social care professionals was published (Royal College of Psychiatrists, 2015). This guide outlined approaches to assessment, treatment and care that included psychosocial interventions, supporting families and carers, as well as legal and ethical considerations. It also covered specialist approaches to substance misuse, such as emergency physical and psychiatric presentations, managing

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withdrawal syndromes, heroin/benzodiazepine misuse in the community, challenges to recovery, and older women with alcohol misuse.

Although the areas of policy and practice have focused largely on alcohol misuse, a later report included illicit drugs, aimed to identify some of the key issues and problems in this area, and make achievable recommendations for change (DrugScope, 2014). A further revision to *Our Invisible Addicts* is currently in preparation, which will also include more recent developments such as the rise in opioid misuse and the potential misuse of gabapentinoid drugs by older people.

Service development for older people with alcohol and other substance misuse

Developing an integrated service for older people with alcohol and other substance misuse requires clinically effective inter-agency working that can minimize harm and improve health and social outcomes. The aims of such a service would be the prevention of alcohol and other substance related mortality (including those with comorbid mental and physical disorders); enhancement of the quality of life of older people and community integration through the provision of high-quality care (Royal College of Psychiatrists, 2015). In addition to mental health service provision, geriatric medicine (Crome et al., 2011), primary care (Rao et al., 2016), social care (Rakshi et al., 2011), the voluntary (third) sector (Holley-Moore and Beach, 2016), local authority (Wilson, 2013), and housing (Giles, 2016) are also key components in enhancing the quality of care for older people with alcohol and other substance misuse.

A key principle in the delivery of non-specialist care within mainstream mental health services is 'making every contact count'. This forms the basis of much of the commissioning for substance misuse services in England (Nelson et al., 2013).

Improving social care is also central to treatment and recovery from substance misuse in older people, where life events such as retirement, bereavement, and social isolation may have a profound impact on social function. Approaches to harm reduction in older people often involve replacing time engaged in substance use with improving social networks and social skills training around refusal of substances in social settings. There is also scope for further social integration, such as attending self-help groups (e.g. Alcoholics Anonymous), increasing family input, encouraging healthy lifestyles and facilitating volunteering activities (Rao, 2015).

One programme providing relapse-prevention and social skills training for older people with alcohol misuse showed higher rates of abstinence compared to the non-completers (Schonfeld et al., 2010).

However, with the complexity in assessment, treatment, and aftercare for older people with alcohol and other substance misuse, there is a need for specialist mental health services that address the needs of older people.

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The first specialist dual diagnosis service for older people with alcohol misuse in the UK was developed at the South London and Maudsley NHS Foundation Trust in south east London, UK (Rao and Shanks, 2011).

The initial development of this service was built on the following strategic aims and objectives and continues to be developed with a dual diagnosis working group. This group now includes a consultant old age psychiatrist, nurse consultant lead for dual diagnosis across the Trust, senior Clinical Academic Group Manager for quality, and modern matron and nurse borough leads. The service has the following aims:

- Building on existing good practice (e.g. referral to and from liaison old age psychiatry and addiction psychiatry services);
- Scoping the need for new services and roles (e.g. delivery of in-patient training to meet Commissioning for Quality and Innovation-*CQUIN* outcomes);
- Creating new service options where possible (predominantly home-based assessment and treatment of dual diagnosis by Community Mental Health Teams);
- Developing clinically effective care pathways (Alcohol, benzodiazepines, tobacco and cannabis) (See Box 46.1);
- Promoting robust partnerships with key stakeholders (e.g. service users and carers group);
- Building a skilled workforce (acquiring relevant competencies through dual diagnosis training);
- Establishing robust communication and reporting structures (e.g. serious incidents, as well as rates of screening and brief intervention);
- Promoting health education, prevention and early intervention for service users.

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Box 46.1 Care pathway for dual diagnosis

- Aligned to other care pathways for dementia, depression, and personality disorders
- Involves patient, care coordinator, multi-disciplinary team, consultant old age psychiatrists, general practitioner, other medical specialties (e.g. geriatrics), social care, and (where relevant) specialist addictions practitioner
- Comprises screening, assessment, engagement, assessing, and facilitating motivation to change, developing an action plan that incorporates harm reduction and recovery, as well as relapse prevention
- Incorporates a care pathway within risk assessment, care management, and review

Conclusions and future directions

More attention has recently been paid to the issues of substance misuse among older people, but there are still significant gaps in our knowledge about the subject. We need more detailed research about gender differences, including different risk factors for addiction in older women, and barriers to treatment. We need a better understanding of the abuse of prescription medication among older people. Alcohol-related cognitive impairment remains an under-diagnosed and often misunderstood area. And we still have limited information about what treatment works best for older people, with no best practice reviews available for individual therapeutic approaches.

We need to focus on the 'at risk' growing population of 'baby boomers' whose patterns of substance misuse are very different from previous generations. This is likely to mean a greater burden of mental health as well as physical and psychosocial need. It will have implications for exploring substance misuse in a wider variety of prescribed and illicit drugs, as well as finding new solutions to developing integrated care through working with multiple specialties and other agencies.

This can only be achieved by having the evidence base to underpin clinically effective treatment interventions that both reduce harm and improve independence and quality of life.

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Older people with intellectual disability

Chapter: Older people with intellectual disability

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Introduction

Older people with intellectual disability (ID) comprise a heterogeneous and clinically complex population to whom little clinical or research interest has been devoted.

Persons with ID and dementia are less likely to receive planned health care than persons with dementia in the general population. They have, however, higher levels of unplanned health care utilization. This clearly indicates that the current support system is not sufficient to meet the challenges of increased longevity among persons with ID (Axmon et al. 2016). The cost of caring for older people with ID makes up a large proportion of healthcare spending in Western Europe. For example, in England older adults with ID comprise about 0.15–0.25% but consume up to 5% of the total personal care budget. It seems very likely that general services for older people will need to prepare themselves for the inclusion

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of this subgroup of the ageing population. This will have huge implications for future planning of services (Strydom, Romeo et al., 2010).

This chapter reviews the concept and diagnostic criteria for ID and its prevalence in older people, and summarizes the present knowledge about functional psychiatric illness and dementia in this group. A separate section concentrates on issues related to Down's syndrome (DS) and the increased risk of dementia in this group, followed by a section on assessment and management of dementia in ID in general, including pharmacological treatment and end-of-life and best-interest decisions, with reference to relevant best practice guidelines.

Definition and diagnostic criteria for intellectual disability

'Mental retardation' and 'learning disabilities' are terms that have been used to describe a disability characterized by significant limitations in both intellectual functioning and in adaptive behaviour, that is manifest before the age of 18. The term 'Mental Retardation' has been replaced by 'Intellectual Developmental Disorder' in the beta draft of the eleventh edition of the World Health Organization's *International Classification of Disease* (ICD-11) published in 2018 (in use for 2022), and by 'Intellectual Disability (Intellectual Developmental Disorder)' in American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) (APA, 2013). The ICD-11 term has been incorporated in brackets in the DSM-5 schedule to indicate that both classification systems use similar diagnostic criteria.

In both classifications ID forms part of the wider diagnostic category of neurodevelopmental disorders. These are categorized according to severity as mild, moderate, severe, and profound.

A diagnosis of ID has to satisfy three diagnostic criteria:

- i) Significantly sub-average intellectual functioning. This is defined as an Intelligence Quotient (IQ) of 70 or below on an individually administered, standardized, and culturally appropriate IQ test (and for infants, a clinical judgment of significantly sub-average intellectual functioning). By definition, 2.5% of the population fall within this bracket.
- ii) Deficits or impairments in adaptive functioning (skills needed to live in an independent and responsible manner). Deficits in adaptive functioning must be measured using standardized, culturally appropriate tests. Deficit or impairment should be present in at least two of these areas: communication, self-care, home living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, and health and safety.
- iii) These limitations are evident during childhood or adolescence, before the age of 18 years.

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Prevalence of intellectual disability in older people

There is no agreed definition of what constitutes 'older' in people with ID. Various age thresholds for the ageing population with ID have been adopted in the literature which range from 40–65 years of age (Jenkins et al., 1994).

Little is known about the prevalence of ID among the general older population. It is estimated that there are 1,198,000 people with ID in England (Emerson, 2011) (approximately 1% of the total population). This figure includes 334,000 individuals with ID over the age of 50 years (37% of the total ID population) and 202,141 over the age of 60 years (22% of the total ID population). It is estimated that a typical GP catchment area of 250,000 population would comprise 2,500 individuals with ID, 925 individuals over the age of 50, and 550 individuals over the age of 60 years.

Approximately 13–20% of the ID population have DS (Hand and Reid 1996) and it has been estimated that there are approximately 40,000 adults with DS in the UK (Wu and Morris, 2013). More than 40% of people with DS in the UK are aged 40 years or older (de Graaf et al. (2011) and one in 10 of these individuals will develop AD over the next 10 years (Livingston and Strydom, 2012). This rate rises to one in three for those who are older than 50 years and more than half for those older than 60 years (Strydom, Shooshtari et al., 2010).

Only a very small number of people with ID are known to services. This is particularly true for older people with ID still being cared for by elderly relatives. These peoples' relatives are from a generation that would have been reluctant to engage with services. Not uncommonly, older people with ID present in crisis when they and/or their own elderly parents develop dementia.

Functional psychiatric disorders in older people with intellectual disability

People with ID of all ages have higher rates of mental ill health than the non-intellectually disabled (Cooper et al., 2007, Hughes-McCormack et al., 2017; Axmon et al., 2017). It is estimated that more than a third of people with ID have associated diagnoses of mental disorders (Pickard et al., 2010). Persons with borderline intellectual disabilities also experience higher rates of mental ill health than the general population, but receive fewer treatments (Cooper and van der Speck, 2009). In a recent study on the prevalence of mental health conditions comparing the population of people with ID with the general population, mental health conditions were reported more often for people with ID than in the general population (Hughes-McCormack et al., 2017). They found that 23.4% of adults (aged 16–64 years) and 27.2% of older adults (aged 65+ years) had mental health conditions compared with 5.3% and 4.5% of people of the same age in the general population, respectively. In this study ID was

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associated with a mental health disorder with a high odds ratio (OR) = 7.1 (95% CI 6.8-7.3). Hughes-McCormack and colleagues (2017) found that increase in age was also associated with increasing odds of a mental health disorder although this was so only until the age of 64 years. The odds plateaued from that age but remained higher than in the general population. This may be due to the death of people with severe/profound ID who have higher rates of mental disorders relative to people with mild/moderate intellectual disabilities.

Cooper and colleagues (1997) compared the prevalence of psychiatric disorder between a randomly selected younger group of people with ID and a group of identified older people with ID (over 65 years old) in a defined geographical area. In the older group, an additional psychiatric disorder was present in 68.7% of people, compared to 47.9% in the younger group. The higher rates of psychiatric diagnosis in the older group were due mainly to a high rate of dementia of 21.6%, as compared with 2.7% in the younger bracket. This high rate was not accounted for by the presence of DS, as the older group included only 3.7% of people with DS, compared with 28.8% of the younger population. The older group also had higher rates of generalized anxiety disorder (9.0% compared with 5.5%) and depression (6.0% vs 4.1%). The presence of behaviour disorders, pervasive developmental disorders, anxiety disorders, and psychotic disorders was equal in both groups. Schizophrenia/delusional disorders were present in 3% (vs 2.7%) and mania in 0.7% (vs 0.0%). There were no cases of obsessive-compulsive disorder or alcoholism. Behavioural disorder was equal in both groups (14.9% vs 15.1%).

Diagnostic criteria for mental disorders used in the general population (ICD-10 and DSM-5) tend to underestimate the prevalence of mental illness in this population, when compared with the Royal College of Psychiatrists Diagnostic Criteria for Psychiatric Disorders for use with adults with Learning Disabilities (DC-LD) (RCPsych, 2001; Cooper et al., 2007), a supposedly more reliable measure.

Mental ill health has been reported to be less prevalent in adults with DS than for other adults with ID (Cooper and van der Speck, 2009). In a longitudinal cohort study of 168 people with DS (mean age = 41.1 years; range = 16-74 years; standard deviation = 11.8 years), Mantry and colleagues (2008) reported a point prevalence of mental ill health of any type, excluding specific phobias, of 23.7% by clinical diagnosis, 19.9% by DC-LD (RCPsych, 2001), 11.3% by ICD-10 criteria, and 10.8% by DSM-IV-TR criteria. Compared with persons with ID not due to DS, the standardized rate for prevalence of mental illness in people with DS was 0.6 (0.4-0.8), or 0.4 (0.3-0.6) if organic disorders are excluded.

Depression has been reported to be the most common mental health problem in people with DS (Määttä et al., 2006) and is often associated with the presence of dementia (Prasher and Filler, 1995). Detection of depression in DS is problematic as people with DS do not tend to verbalize symptoms of depression and the diagnosis is often inferred from

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the presence of prominent vegetative symptoms and, on occasions, by auditory hallucinations (Myers and Pueschel, 1991).

Dementia in intellectual disability

Definition and diagnostic criteria for dementia in intellectual disability

There is no definition of dementia that is specific for individuals with ID. The use of the ICD-10 (WHO, 1992) criteria for the diagnosis of dementia in people with ID has been supported in preference to the DSM-IV (APA, 1994), because the ICD-10 criteria place more emphasis on 'non-cognitive' aspects of dementia, which have often been reported to be part of the first signs of dementia in people with ID (Aylward et al., 1997). In 2001, the Royal College of Psychiatrists modified the ICD-10 diagnostic criteria for dementia for use with people with ID in publishing the DC-LD (RCPsych, 2001). However, Strydom and colleagues (2007) examined the validity of the three dementia diagnostic criteria in an epidemiological sample of older adults with ID not due to DS, showing that DSM-IV dementia criteria were more inclusive than DC-LD or ICD-10, and that diagnosis using ICD-10 excluded people with even moderate dementia. It is clear that both schedules are imperfect (Sheehan et al., 2015).

Dementia in the ID population, as in the general population, is a clinical diagnosis that requires the expertise of a clinician with experience in assessing cognitive and functional decline. A recent study by Sheehan and colleagues (2015) compared concurrent validity and reliability of clinicians' diagnoses of dementia against ICD-10 and DSM-IV-TR diagnoses. Validity of clinical diagnoses were also explored by establishing the stability of diagnoses over time. They used clinical data from memory assessments of 85 people with DS, of whom 64 (75.3%) had a diagnosis of dementia. The cases of dementia were presented to expert raters who rated the cases as dementia or no dementia using ICD-10 and DSM-IV-TR criteria, but the raters also rated the cases according to their own clinical judgment. The authors found that the clinicians' judgment corresponded best with clinically diagnosed cases of dementia, identifying 84.4% cases of clinically diagnosed dementia at the time of diagnosis, as opposed to ICD-10 criteria (70.3% of cases) and DSM-IV-TR criteria (56.3% of cases). Over time, the proportion of cases meeting ICD-10 or DSM-IV-TR diagnoses increased, suggesting that experienced clinicians used their clinical knowledge of dementia presentation in DS to diagnose the disorder at an earlier stage than would have been possible had they relied on the descriptions included in the diagnostic systems.

In the beta draft of the ICD-11 there is a specific code for Dementia due to DS, 6E35.8, under 'Dementia due to diseases classified elsewhere'. This is included in the category of 'Neurocognitive Disorders'. This code does not define or give diagnostic criteria for dementia in DS but simply describes it as:

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Dementia due to Down syndrome, a chromosomal abnormality syndrome, typically associated with Alzheimer disease neuropathological changes. It occurs most commonly after the fourth decade.

Difficulties in the diagnosis of dementia in intellectual disability

Owing to the high rates of physical and mental ill health as well as sensory and mobility impairment in this population, cognitive and functional decline arising from the ageing process can be difficult to distinguish from early signs of dementia.

Given the wide range of abilities in the ID population it is not possible to make a diagnosis of dementia from examining an individual on one occasion. A diagnosis of dementia requires evidence of deterioration in functioning in the individual in question. Longitudinal assessments that document both baseline and present cognitive and behavioural functioning over a period of at least six months is necessary before sufficient information can be obtained to make a confident diagnosis of dementia (Burt and Aylward, 1998).

The clinical picture of decline in cognitive function and behaviour in individuals with mild ID who develop dementia is not dissimilar to that seen in the general population with Alzheimer's disease (AD). However, in people with severe and profound ID, given their extremely limited cognitive and independent functional skills, a diagnosis of dementia is consequently uncertain (Strydom et al., 2009).

To be indicative of dementia, any changes found over time must be greater than those related to normal ageing in adults with ID (Burt and Aylward, 1999). People with ID as a whole tend to age faster and to show signs of 'ageing' earlier than the general population (Jenkins et al., 1994). There is little information regarding the impact of ageing in this population.

Functional ability decreases with age in individuals with ID, but, when examined as a group, functional ability apparently improves in later life. This is very likely an artefact arising because of differential mortality rates, as shorter life expectancy is found in people with more severe learning disabilities and in people with DS (Moss, 1991). Day and Jancar (1994) summarized the extent to which physical disabilities contribute to age-related morbidity in people with ID, as have Haveman and colleagues (2011) more recently. These studies report an increasing prevalence of musculoskeletal, cardiovascular, respiratory, and neoplastic illnesses with age. However, in the case of some disorders (e.g. neoplasia), age-related increases in prevalence are relatively small. Cataract, hearing disorder, diabetes, hypertension, osteoarthritis/arthrosis, and osteoporosis were more strongly associated with advancing age, whereas allergies and epilepsy were negatively associated.

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Standard cognitive screening tools are inappropriate to use in the ID population as those people with moderate, severe, and profound handicaps will score zero or very low. This is known as the floor effect. It is possible to obtain information from people caring for this population but there is a high turnover of staff in settings where people with ID live and it is often difficult to obtain a reliable informant who has known the individual with ID for long enough to be able to comment on any change in performance.

The assessment of cognitive function in this population is considered in Cognitive tests.

Dementia in people with intellectual disability not due to Down's syndrome

It is established that people with DS tend to develop dementia more often and at an earlier age than the general population. It is generally less well known that people with ID not due to DS also suffer from dementia at higher rates and at an earlier age than those who do not have ID (Thompson, 1951; Tredgold, 1952; Patel et al., 1993; Strydom et al., 2009). Dementia is four times more common in older persons with ID without DS than in the general population (Cooper and Speck, 2009).

Incidence, prevalence, types of dementia, and risk factors

Strydom and colleagues (2013) estimated the incidence rates of dementia from a longitudinal study of dementia in older adults with ID without DS and compared them with general population rates. A total of 222 participants with ID without DS aged 60 years and older were followed up for an average of 2.9 years to identify those who had declined in functional or cognitive abilities. Those who screened positive had a comprehensive assessment for dementia, diagnosed using ICD-10 and DSM-IV criteria. A total of 134 participants who did not have dementia at initial assessment were alive and interviewed at follow-up, and of these 21 (15.7%) were diagnosed with dementia. Overall incidence rate for those aged ≥ 60 was 54.6/1000 person years (95% CI 34.1–82.3). The highest incidence rate (97.8/1000 person years) was in the age group 70–74. The standardized incidence ratio for those aged ≥ 65 was 4.98 (95% CI 1.62–11.67).

Strydom and colleagues in an earlier study in 2009 estimated the prevalence of dementia in people with ID not due to DS in a group of 281 individuals aged 60 years or over using defined diagnostic criteria for 'probable' subtypes of dementia. Overall, prevalence for criteria-defined dementia was 13.1% in those aged 60 years or over and 18.3% in those aged over 65 years. AD, diagnosed using NINCDS-ADRDA criteria (McKhann et al., 1984), was the most common type of dementia, with a prevalence of 8.6% in those of 60 years and over and 12% in those over 65 years. Dementia with Lewy bodies, diagnosed using the McKeith and colleagues (1996) criteria, was the second most common diagnosis, with a prevalence of 5.9% in those of 60 years and over and 7.7% in those over

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65 years. Frontotemporal dementia, using the McKhann and colleagues (2001) criteria, was 3.2% in those of 60 years and over and 4.2% in those over 65 years and was more common than vascular dementia diagnosed using the NINDS-AIREN criteria (Roman et al., 1993) (2.7% in those of 60 years and over and 3.5% in those over 65 years). Prevalence rates did not differ between mild, moderate, and severe ID groups. Age was a strong risk factor for dementia and was not influenced by gender or ID severity.

Clinical presentation

Despite problems in diagnosing dementia in this group, there are significant measurable differences in several neurocognitive domains between people with ID with and without dementia. Test performance on measures of attention and executive functions, language, memory, and learning have been reported as significantly lower for persons with ID and dementia compared with matched controls of people with ID without dementia (Palmer, 2006).

There is some evidence that the clinical presentation of dementia may differ between people with ID and DS and those with ID due to other causes. Cooper and Prasher (1998) conducted a small study comparing a group of 19 people with DS and dementia, and a group of 26 people with ID from other causes who also had dementia. Maladaptive behaviours and psychiatric symptomatology were assessed in both groups. The group with DS had a higher prevalence of low mood, restlessness and overactivity, disturbed sleep, lack of cooperation, and auditory hallucinations. Aggression occurred with greater frequency in those subjects with ID not due to DS.

Assessment of dementia in people with learning disabilities

The psychiatric assessment of people with ID is complicated, given the potential communication difficulties displayed by this group (Sigelman et al., 1981). In the older person with ID, this is even more difficult as a result of added age-related sensory and cognitive difficulties and often a lack of collateral information from carers who have known the person for a sufficiently long period of time (Holland, 2000).

For most people with ID, the assessment of dementia should follow the same process as in the general population, as recommended in the National Institute for Health and Clinical Excellence and the Social Care Institute for Excellence (NICE/SCIE) guidelines on dementia (2006) and on the Royal College of Psychiatrists and British Psychological Society joint guidance on assessment and management of dementia in LD (2015). The aim is to gather a history and evidence of cognitive and functional decline consistent with a diagnosis of dementia and to exclude any physical or mental/emotional causes.

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Physical investigations should be performed in the same way as in the general population (Salem et al., 2015). EEG studies show a correlation between cognitive decline and changes in the EEG in people with DS. The changes include absence or a very slow alpha rhythm at the onset of cognitive deterioration (Evenhuis, 1990), decrease in frequency of the dominant occipital activity (Visser et al., 1996; Velikova et al., 2011), and increase in power in the delta and theta bands, with a decrease in beta and alpha power (Angeleri et al., 1997). These changes can also be seen in EEGs of older people with established dementia.

Environmental assessment is important, as many people with ID and a suspected dementia may still be living with their older parents. It is not uncommon for middle-aged people with ID to have become carers for their older parents, who on some occasions may themselves have dementia. Even for those people who are in care, an environmental assessment is essential as the physical environment, the staff, or fellow residents may be unsuitable for residents with dementia.

Cognitive tests

When diagnosing dementia in adults with ID, the focus should be to recognize decline in cognitive and behavioural function relative to premorbid level of functioning. Three types of tests are used to help with the diagnosis of dementia in people within this group: i) those that rely on direct assessment of the individual, ii) those administered to informants, and iii) those that combine direct cognitive tests and informant reports in the form of a test battery. No single test is sufficient to make an adequate assessment and it is recommended that a behavioural assessment, using the Adaptive Behaviour Scale or similar instrument, should be used in conjunction with both subjective and informant-based tests, particularly in those subjects with severe and profound impairment (Elliott-King et al., 2016)

Subject-based assessments

Direct assessment or subject-based tests include the Prudhoe Cognitive Function Test (PCFT) (Kay et al., 2003), The Test for Severe Impairment (TSI) (Albert and Cohen, 1992), the Severe Impairment Battery (SIB) (Saxton et al., 1990), and the Adaptive Behaviour Dementia Questionnaire (ABDQ) (Prasher et al., 2004).

The PCFT covers the major domains of cognitive functioning, which are usually examined when testing or screening normal adults for dementia, i.e., orientation, recall, language, praxis, and calculation, some of which are divided into further subdomains. Administration of the PCFT takes no more than 45 minutes but there are two shorter versions that only take ten minutes to administer and have extremely good correlations (more than 0.97) to the longer version (Tyrer et al., 2010), so the shorter versions are preferred.

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The PCFT is a highly reliable instrument with excellent temporal stability. Inter-rater and test-retest reliability are both excellent ($ICC = 0.99$ for both) (Margallo-Lana et al., 2003), but there is a floor effect in the more intellectually disabled. It is recommended that a behavioural assessment, using the Adaptive Behaviour Scale or similar instrument, should be used in conjunction with this test, particularly in those subjects with severe and profound impairment (Elliott-King et al., 2016). The PCFT has been validated against The Kaufman Brief Intelligence Test (K-BIT), an instrument that has been utilized widely to assess cognitive abilities in people with intellectual disabilities. Comparison of performance on the long PCFT in 167 subjects with equal representation of mild, moderate, and severe ID showed high correlations between the verbal and performance sections of the K-BIT with correlation coefficients of 0.85 and 0.78, respectively.

The PCFT has face validity in terms of the acceptability of test items to both user and subjects. It also has content validity as the test questions are representative of the skills in the specified domains of the test.

The TSI was originally designed to assess people with severe dementia in the general population. However, it has particular value for those with more severe levels of ID. The test takes approximately 10 minutes and has no significant ceiling or floor effect (Tyrrell et al 2001). It includes assessment of motor performance, language production and comprehension, memory, conceptualization, and general knowledge. Only eight out of the 24 items available require the person to answer a question verbally. The test has good internal consistency ($\alpha = 0.89$) and excellent inter-rater and test-retest reliability ($\rho = 0.97$ and $\rho = 0.98$, respectively). Inter-rater and test-retest reliability are also good among those with severe ID ($\rho = 0.81$ and $\rho = 0.84$, respectively) (Cosgrave et al., 1998). The TSI was designed to assess people with severe dementia in the general population whose MMSE score is <10 out of 30. The test takes approximately ten minutes and the level of difficulty of the TSI is such that most persons with moderate to severe ID should be able to achieve a measurable score unless they are in an advanced stage of dementia.

The SIB was developed to assess a range of cognitive functioning in patients in the general population with severe dementia who are unable to complete standard neuropsychological tests. There have been three versions of the test and a recently published short version. The test has been translated and validated in Korean, Italian, Spanish, and French populations. It relies on direct assessment of the individual and takes into account the specific behavioural and cognitive deficits associated with severe dementia, allowing for non-verbal or partially correct response such as matching. It is brief, taking approximately 30 minutes to administer (15 minutes for the short version). It is composed of simple one-step commands which are presented in conjunction with gestured commands. The SIB is divided into six subscales: attention, orientation, language, memory, visuospatial ability, and construction. There are also

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brief evaluations of praxis and requests for the patient to respond appropriately when his/her name is called (orientation to name).

The psychometric properties of this scale have been assessed in people with DS with and without dementia. Witts and Elders (1998) concluded that the SIB has a good test/re-test reliability and criterion validity and that in general terms it is suitable for the neuropsychological cognitive assessment of adults with DS.

The Adaptive Behaviour Dementia Questionnaire (ABDQ)

The ABDQ was developed by Prasher, Farook, and Holder in 2004 as a screening questionnaire for dementia in adults with DS. For the development of the ABDQ, one hundred and fifty adults with DS (mean age 44.0 ± 1.46 , range 16-76) were assessed on baseline by review of previously reported intelligence tests, previous level of functioning as determined by review of medical notes, from carer interview and from the mental state examination; severity of the ID was classified using ICD-10 criteria. All persons were followed up on an annual basis as part of ongoing clinical care with detailed reassessments of their physical and mental health, adaptive behaviour, and social needs. Findings for the absence or presence of dementia were compared to changes in the ABS measurements over the five years follow-up to determine which items of the ABS best correlated with deterioration in intellectual functioning and could be subsequently used to develop a screening questionnaire.

The ABDQ is a brief questionnaire with good validity and inter-rater reliability. The ABDQ has been developed from over ten years of research investigating changes in adaptive behaviour in adults with DS. It can be used for all adults with ID irrespective of the severity of ID and dementia. Once the baseline level of independent functioning of a particular person has been established with the full ABS, the ABDQ appears to be a useful instrument for the ongoing assessment of people with DS. It may be most appropriately used in combination with an informant-based schedule,

Informant-based scales

The most widely used informant scales in assessing dementia in this population are the Dementia Questionnaire for People with Learning Disabilities (DLD)—originally called the DMR (Evenhuis et al., 2007), and the Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID) (Deb et al., 2007).

The DLD is an informant-based questionnaire about symptoms of dementia. It consists of 50 items divided in two subcategories: i) cognitive scores and ii) social scores. It is scored by an informant who knows the patient well and covers the person's behaviour over the previous two months. This test was specifically designed for use with people with ID and when used together with standardized tools, it has been useful in providing important information for clinicians assessing dementia in people with ID. The test, however, has some drawbacks. The instrument is

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less sensitive for assessing individuals with dementia in the severe and profound ranges of ID who may never have been able to perform many of the skills assessed in the questionnaire. Evenhuis (1992) has pointed out that it is difficult to discern sensitivity of the DLD when used with depressed individuals and they recommend the use of additional tools. Elliott-King and colleagues (2016) state that it is necessary to use a scale that rates behaviour when using the DLD as the DLD itself does not cover the full range of factors affected by the dementing process. Although the author reported results for single cross-sectional scores, Evenhuis (1996) recommended that score changes over time should be the most valid criterion, as single assessment cut-off scores could be inaccurate. Cut-off scores for dementia should be used cautiously and in conjunction with information gathered from other neuropsychological instruments.

Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID)

The DSQIID is an observer-rated questionnaire, which is completed by carers of people with DS who have known the individual for some time. It has three parts. The first asks about the 'best' ability the person has or has had. The second contains 43 questions about behaviour or symptoms that are usually associated with dementia in adults with DS. Each item is scored on a four-point scale: 'always has been the case'; 'always, but worse'; 'new symptoms'; and 'does not apply'. Items with a response of 'always been the case' or 'does not apply' are scored 0, those with 'always but worse' or 'new symptom' are scored 1. The third part of the DSQIID contains ten questions, all of which are comparative; for example, 'speaks (signs) less' and 'seems generally more tired'. A response of 'yes' is scored 1 and a response of 'no' is scored 0. Scores from parts 2 and 3 are added to provide a total score.

The 53 items of the DSQIID cover areas such as loss of memory, confusion, loss of skills, social withdrawal, behavioural changes, psychological symptoms, physical symptoms, sleep disturbance, and speech abnormalities. The questionnaire takes 10–15 minutes to administer and has a fixed cut off of 20. It has excellent internal consistency (average $\alpha = 0.91$) as well as inter-rater (ICC = 0.90) and test-retest reliability (ICC = 0.95). However, its fixed cut-off may compromise its usefulness in people with more severe ID or advanced dementia (O'Caoimh and Molloy, 2013).

Deb and colleagues (2007) indicate that to avoid the floor effect, the DSQIID has a scoring system by which only recent changes in behaviour are scored rather than all behaviours, which allows the use of the DSQIID in a cross-sectional context. However, it is probably best used at regular intervals over a period of time to identify the change in score. The DSQIID has been administered to over 800 patients over numerous studies and all found it to be informative (Elliott-King et al., 2016).

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Communicating the diagnosis to patients and carers

Ideally, every effort should be made to share information with the person with ID and dementia, perhaps recruiting the assistance of a speech and language therapist (SALT) to make the information as 'user friendly' as possible (Royal College of Psychiatrists and British Psychological Society, 2015). However, in practice this is at times not feasible as many people do not have adequate cognitive ability to understand what is being said and such attempts could result in the person becoming distressed.

Because of difficulties in communication with the individual with ID it is very important that carers and family are involved during the assessment process and that information about the outcomes, diagnosis, and care plans are shared with them. Sensitive handling of their own emotional response to the information given will be necessary to maintain their engagement at all stages, particularly at the end-of-life phase.

Dementia in people with Down's syndrome

DS is the commonest cause of early-onset dementia generally and particular attention to the manifestations of dementia in this genetic disorder are considered here.

It is not common for this illness to arise before the age of 50 but Holland and colleagues (2000) found that 40% of those aged over this age had developed dementia. Adults with DS have a high prevalence of AD type dementia and low rates of vascular dementia. They are resilient to atherosclerosis (Ylä-Herttuala et al., 1989) and have low blood pressure and slow pulse (Cooper et al., 2016). While rare, cases of Lewy body dementia and frontotemporal dementia have been reported (Raghavan et al., 1993).

The association between dementia and DS was first scientifically reported by Fraser and Mitchell (1876), well before Alois Alzheimer described the case of the first patient with the disease that later bore his name (Alzheimer, 1907). It was Jervis who in 1948 first clinically described the association between DS and AD (Jervis, 1948).

The reason why dementia occurs more frequently in individuals with DS is still not known definitively. However, it is well-recognized that people with DS have a genetic predisposition to develop this type of dementia due to the triplication of the APP gene on chromosome 21, leading to overproduction and deposition of amyloid beta (A β). Further information on this relationship is covered later in this chapter (see also APP, BACE-1, and BACE-2).

Prevalence

DS is the most commonly identified genetic form of LD and the leading cause of specific birth defects and medical conditions (Sherman et al., 2007). The prevalence of DS for the 16 years and over population in the

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UK has been reported as 5.9 per 10,000 general population (Mantry et al., 2008). Within this population the prevalence of dementia among adults with DS has been estimated to be approximately 20% after the age of 40 (Janicki and Dalton, 2000) and 45% after the age of 55 (Silverman et al., 1998). After the age of 60, approximately half of individuals with DS have a diagnosis of dementia (Janicki and Dalton, 2000; Margallo-Lana et al., 2007).

A rather more optimistic outlook for this population has been reported by Coppus and colleagues in the Netherlands (2006) in the largest longitudinal study published yet. Their study included 506 people with DS over the age of 45 years who were followed-up for a mean period of 3.3 years. They reported an overall prevalence of dementia of 16.8%. Up to the age of 60, the prevalence of dementia doubled with each five-year interval. From age 45–49, the prevalence was 8.9%, from 50–54, it was 17.7%, from 55–59, it was 32.1%, and from 60 and above, it was 25.6%. The authors argued that the lack of increase in prevalence after the age of 60 may be explained by the increased mortality among older DS patients in comparison with patients without dementia and this belief was supported by the finding that there was no decrease in the incidence of dementia in the age group of 60 and above. In a 15-year follow-up community study of 92 people with DS who had previously been institutionalized, the years at risk for dementia for those aged 45 or under was found to be zero, whereas it reached a maximum of 7.5/100 person years in those aged over 60 years (Margallo-Lana et al., 2007).

Despite greater awareness of the risks of DS, the incidence of births of babies with this condition have barely altered over a ten-year period (Morris and Alberman, 2009).

Life-expectancy and mortality

Life-expectancy of individuals with DS has increased in the last 60 years from 12 years of age in 1949 to nearly 60 today (Penrose, 1949; Bittles and Glasson, 2004). However, life-expectancy in people with DS is still lower than in the general population and remains lower than in people with ID who do not have DS.

Clinical presentation

The clinical presentation of dementia in people with DS is influenced by the severity of handicap. The milder the severity of disability, the closer the symptomatology will be to that seen in the general population with AD.

In this less-severely handicapped population, forgetfulness, impairment of recent memory with relatively intact long-term memory, and confusion are all common, and present early in dementia among adults with DS. A general slowness in activities and speech, language problems, loss of interest in activities, social withdrawal, balance problems, sleep difficulties, and loss of pre-existing skills, along with the emergence of

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emotional and behavioural problems, are common presentations of dementia among adults with DS (Deb et al., 2007). Some studies have suggested that people with DS tend to have early manifestations of frontal lobe symptomatology rather than memory changes (Ball et al., 2010). This is not surprising, given the brain developmental abnormalities present in people with DS at birth affecting the frontal lobe (Teipel and Hampel, 2006), and the fact that the earliest deposition of A β in the brain of people with DS occurs in the frontal lobe and entorhinal cortex (Azizeh et al., 2000; Nelson et al., 2011).

Among adults with more severe and profound ID, the diagnosis of dementia, in the absence of any measurable cognitive decline, needs to be made on the basis of behavioural changes characteristic of progressive neurodegenerative disease. These include features such as daytime sleepiness, wandering, decreased mobility, onset of epilepsy, increased incontinence (Burt et al., 1992; Margallo-Lana et al., 2007), abnormality of the posture or gait (Lai and Williams, 1989), and rigidity or myoclonic jerks (McVicker et al., 1994). These symptoms support the diagnosis of dementia when cognitive decline cannot be reliably measured.

Cognitive changes associated with dementia in Down's syndrome

As previously described, those people with DS who have mild to moderate handicaps show similar patterns of cognitive impairment when a dementing illness arises to non-handicapped individuals from the general population who develop dementia.

The cognitive profile of people with DS and dementia was recently compared with that of people with AD in the general population by Dick and colleagues (2016) using the Severe Impairment Battery (SIB) (Saxton and Swihart, 1989)). Fifty-one individuals without ID who had moderate to severe dementia and 59 people with DS and dementia were assessed, controlling for gender as well as level of functional ability using a modified version of the Bristol Activities of Daily Living Scale. Overall, the neuropsychological profiles of the higher-functioning individuals within the DS group and individuals with moderate to severe dementia from the general population groups, were very similar to one another, after adjusting for gender and functional impairment, when the total scores and the nine separate domains of the test were compared.

The assessment of cognitive change in the DS population has been covered in the previous section concerned with the assessment of cognition in the ID population. A number of instruments and schedules were covered earlier (see Cognitive tests) and those that have been expressly designed for individuals with DS, e.g. the PCFT and the DSQUID are recommended.

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Behavioural changes

Behavioural changes are common in people with DS in the early stages of dementia (Määttä et al., 2006). People with DS and dementia tend to display less aggressive behaviour but greater degrees of depression, restlessness, hyperactivity, disturbed sleep, oppositional behaviour, and auditory hallucinations compared to people with ID from other causes who develop dementia. (Cooper and Prasher, 1998). Nonetheless, in comparison with patients with AD, people with DS and dementia have fewer problem behaviours.

Other symptoms often associated with dementia in people with Down's syndrome

Epilepsy

People with DS have a triphasic distribution of epilepsy incidence, with peaks in childhood, early adulthood, and in late middle age (Pueschel et al., 1991). Up to 84% of people with DS and dementia will develop epileptic seizures over time (Puri et al., 2001). These seizures tend to occur early in the course of dementia and respond well to treatment (Gholipour et al., 2017; McCarron et al., 2017). In addition to generalized epileptic seizures, individuals with DS who develop dementia often demonstrate myoclonic seizures, described as Late Onset Myoclonic Epilepsy in Down's Syndrome (LOMEDS) (Möller et al., 2001). LOMEDS is characterized by a progressive deterioration of cognitive function a few years before the onset of the epilepsy, featuring myoclonic as well as generalized tonic-clonic seizures (Li et al., 1995). EEG changes show generalized fast spike-waves or polyspike-waves with or without bilateral myoclonic jerks, especially on wakening. Photo paroxysmal response (11–21 Hz) has also been described as part of LOMEDS (Crespel et al., 2007).

D'Orsi and Specchio (2014) studied the natural history of myoclonic epilepsy associated with dementia in adults with DS. Twelve patients with DS over the age of 40 years with myoclonic epilepsy underwent clinical, neuropsychological, neurophysiological, and neuroradiological studies. Three main phases appeared during the course of the syndrome, which occurred over a short period of time. The first stage was characterized by onset of dementia (mean age: 51 ± 6.6 years), diffuse EEG abnormalities during sleep, and cerebral atrophy determined by neuroimaging. During the second stage, myoclonic epilepsy was manifest (mean age: 51.4 ± 7.2 years) with myoclonic jerks time-locked to diffuse epileptiform abnormalities upon wakening. At the time of the third stage (mean age: 54.8 ± 7.6 years), myoclonic seizures were replaced with non-epileptic myoclonus, and cerebellar signs, severe dementia, and the development of photosensitivity.

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Dysphagia

There is no published research examining the effect of dementia on drinking, eating, and swallowing in adults with DS (Lazenby, 2008). All degenerative diseases affecting the central nervous system are associated with feeding problems as the disease progresses. People with DS have specific oropharyngeal problems (Hennequin et al., 1999), swallowing dysfunction (Frazier and Friedman 1996), high prevalence of oesophageal motor disorders (Bianca et al., 2002), and increased prevalence of reflux (Wallace, 2007), which increase the risk of dysphagia and aspiration. Progressive dysphagia and frequent choking may be observed in people with DS in the early stages of dementia but are more obvious in the middle stage (Alvarez, 2011). Dysphagia may not be diagnosed until the patient presents with severe weight loss or recurrent respiratory infections.

Motor/gait disorders and falls

When people with DS develop dementia, motor disorders manifest early in the disease but usually become more obvious in the middle and advanced stage of the illness. The symptoms include general motor slowness, difficulty in performing complex motor tasks, e.g. getting in and out of a car, going up and down stairs, negotiating changes in levels e.g. kerbs by pavements, progressive gait disorder, falls, and, in some patients, parkinsonian symptoms (Alvarez, 2011). In the advanced stages patients become bedridden, with little voluntary movement.

There is little research on falls and motor disorders in older people with DS and dementia. Although it has been reported that young people with DS have a lower risk of falling compared with their peers having other types of ID (Finlayson et al., 2010), others have found that increased age on its own is a risk factor for falls generally among the ID population, including people with DS (Cox et al., 2010).

Natural history

There is little research devoted to the natural history of dementia in people with DS. In the 15-year follow-up study of 92 people with DS mentioned in the Prevalence section (Margallo-Lana et al., 2007), the mean age of onset of dementia was 55.5 years (range 45–74) and the mean age of death with dementia was 59.1 ± 9.6 years, with a survival period from onset of dementia until death of 3.5 ± 2.2 , range 1–8 years. The majority of deaths were due to bronchopneumonia. Respiratory tract infection is a common reported cause of death in older people in general, in the general population with AD (Keene et al., 2001), and has previously been reported as a common cause of death of people with DS and dementia (Evenhuis, 1990).

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Age-related changes in physical health

Adults with DS experience premature age-related health problems (see Esbensen, 2010 for a comprehensive review). Among these, apart from the increased risk for dementia, are skin and hair changes (Madan et al., 2006), early-onset menopause (Seltzer et al., 2001), visual and hearing impairments (McCarron et al., 2005), adult-onset seizure disorder (Menéndez, 2005), thyroid dysfunction (Coleman, 1994), obesity (Melville et al., 2005), sleep apnoea (Resta et al., 2003), testicular cancer (Hasle et al., 2000), musculoskeletal problems such as osteoporosis, osteoarthritis, decreased muscle strength, impaired balance, falls (Dacre and Huskisson, 1988), and mitral valve prolapse (Barnhart and Connolly, 2007). There are conflicting reports about whether people with DS are at increased risk of diabetes type 1 (Haveman et al., 1989; Yang et al., 2002; Hill et al., 2003) and decreased risk of diabetes type 2 (Silverman, 2010).

Adults with DS are at a lower risk than the general population for several medical conditions, including malignant solid tumours (Satgé et al., 1998), cerebrovascular and non-congenital cardiovascular disease (Marino and Pueschel, 1996), and digestive system disease (Glover and Ayub, 2010). They have lower resting heart rates and lower blood pressure than the general population (Prasher, 1994). Hypertension is not common in this population (Kerins et al., 2008). Compared with people with ID not due to DS, they have lower rates of emphysema, fractures, and hypercholesterolaemia (Kerins et al., 2008). While significant respiratory problems are not common (Minihan and Dean, 1990), as mobility declines with age, recurrent pneumonia with incomplete recovery has been found to occur more often than in the general population (Van Allen et al., 1999). This is significant as respiratory illness is a common cause of mortality in adults with DS (Margallo-Lana et al., 2007; Esbensen, 2010).

Age-related cognitive changes

Cognitive decline occurs relatively early in DS and is naturally more common than dementia (Carr and Collins, 2014). Several studies have compared the cognitive profile of older people with DS without dementia to young DS and older people with DS and dementia (Haxby, 1989; Schapiro et al., 1992). These investigations have shown that older people with DS without dementia do not differ from the younger DS groups on tests of overall abilities, such as the Stanford-Binet Test (Terman and Merrill, 1973), tests of attention or language (Schapiro et al., 1992), and immediate verbal memory spans (digit and object pointing spans). Older people with DS without dementia did have lower visuospatial memory span (block tapping) than younger DS subjects. This suggests that there is a greater loss of immediate visuospatial memory compared with immediate verbal memory during the ageing process in DS even in the absence of dementia. Age-related changes in verbal communication in people with DS include a decline in social discourse involving changes in

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conversational style, literal understanding, and verbal expression in social contexts (Nelson et al., 2001; Couzens et al., 2011).

Other studies looking at measures of attention, executive function, and memory in people with DS without dementia suggest that people with DS over the age of 40 experience an average annual global cognitive decline of 11%, indicating that progressive cognitive decline occurs from midlife onwards, even in the absence of dementia (Margallo-Lana et al., 2003).

Ghezzi and colleagues (2014) in a cross-sectional study of age-related cognitive and adaptive changes of a group of 67 persons with DS without dementia, of different ages (11 to 66 years), found that both neuropsychological function and adaptive skills are lower in adult DS persons over 40 years old, compared to younger ones. In particular, language and working memory skills, frontal lobe function, visuo-spatial abilities, and adaptive behaviour appear to be the more affected domains. A growing deficit in verbal comprehension, along with social isolation, loss of interest and greater fatigue in daily tasks, are the main features found in older, non-demented DS persons evaluated in this study. These signs are the harbingers of incipient dementia.

Age-related changes in functional skills

The literature about age-related changes in functional skills for people with DS without dementia is controversial. Although Esbensen and colleagues (2008) found evidence of age-related change in a longitudinal study over nine years in a group of 150 adults with DS and 240 adults with ID due to other causes, Dressler and colleagues in 2010 detected no major decline in middle adulthood in a study involving 75 individuals with DS without dementia.

Risk factors for development of dementia in Down's syndrome

Age

As in the general population, age is the strongest risk factor influencing the age of onset of dementia in people with DS (Bush and Beail, 2004; cited in Zigman and Lott, 2007).

Gender

The existing literature regarding rates of dementia according to gender shows conflicting results. For example, Schupf and colleagues (1998) reported that, compared with women, men with DS are three times as likely to develop AD. In contrast, Lai and colleagues (1999) found that women were 1.77 times as likely to dement as men at any given point in time ($P = 0.04$).

There does, nevertheless, seem to be a significant relationship between age of onset of menopause and the onset of dementia (Schupf et al., 2006; Coppus et al., 2010) in women with DS. Coppus and colleagues (2010)

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recently reported that early age at menopause is associated with a 1.8-fold increased risk of dementia.

APP, BACE-1, and BACE-2

APP is expressed at levels that are four- to fivefold higher in DS than in the general population (Beyreuther et al., 1993). A β peptide is generated from APP by sequential action of β secretase amyloid precursor protein cleaving enzymes 1 and 2 (BACE1 and BACE2) and γ secretase. It has been reported that APP C99, the major β secretase product, and A β are increased in DS (Busciglio et al., 2002; Sun et al., 2006). The gene for BACE2 is located on chromosome 21, probably within the obligate region for DS (Korenberg et al., 1990). BACE2 protein levels have been found to be higher in foetal tissue of individuals with DS (Barbiero et al., 2003) and in fibroblasts of adults with DS, compared with controls from the general population (Motonaga et al., 2002; Barbiero et al., 2003). However, the roles of BACE1 and BACE2 in the neuropathogenesis of AD in DS have been questioned (Sun et al., 2006; Cheon et al., 2008). It has been reported that APP overexpression seems to be absent during the development of the DS brain up to weeks 18–19 of gestational age but is expressed in adult DS brains and it has been confirmed that increased gene expression of APP is associated with the diagnosis of dementia (Schupf et al., 2010). The comparable expression of BACE1 and BACE2 in brains of adults with DS during early foetal brain development contradicts the hypothesis that increased β secretase results in (or even underlies) increased production of amyloidogenic A β fragments in people with DS (Cheon et al., 2008).

Apolipoprotein E4

The literature about the effect of apolipoprotein E (apoE) on AD in DS is inconclusive (Coppus et al., 2008). Bálint and colleagues (2000) studied a group of 56 ethnically homogeneous Hungarian people, looking at the apoE distribution in amniotic fluid of 15-week conceptuses with trisomy 21 from a genetic screening programme, thus including those that might have not reached full-term gestation. The authors found no significant difference in the distribution of apoE alleles in the group of trisomy 21 fetuses compared with samples of blood from healthy blood donors in the same geographical area.

It has been reported that E4 allele frequency of older DS patients is about half that of younger ones, suggesting premature death of people with DS of those with this allele (Folin et al., 2003). ApoE2 has been associated with increased longevity and decreased frequency of dementia in the adult population (Royston et al., 1994) but this allele only occurs in less than 2% of the population. As the majority of studies have found that the apoE allele distribution in people with DS is similar to that found in the general population without AD (Hardy et al., 1994; van-Gool et al., 1995)

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the evidence for a reduced development of dementia in DS subjects possessing this allele is inconclusive because of the low numbers.

Despite the low frequency of apoE4 in earlier studies, several authors (Deb et al., 2000; Coppus et al., 2010; Zigman et al., 2005) have found that on meta-analysis the frequency of apoE4 was higher in adults with dementia compared with adults with DS without dementia, but there was no significant reduction in the frequency of apoE2, although the numbers were small. They concluded that apoE4 influences the age of onset of dementia and mortality risk in DS.

Gene polymorphisms

A gene polymorphism in the prion protein gene has been reported to be associated with earlier decline in intellectual ability in adults with DS (Del Bo et al., 2003). Margallo-Lana and colleagues (2004) reported a 13-year difference in the age at onset of dementia in DS associated with the number of tetranucleotide repeats on intron 7 alleles in the APP gene. The results suggested that APP is an important locus predicting the age at onset of dementia in people with DS.

Atypical karyotypes

Translocations, partial trisomies, and varying degrees of mosaicism are reported to be associated with better survival and lower risk of AD than the full trisomy 21 (Schupf and Sergievsky, 2002). There have been cases reported in the literature of people with DS of advanced age who died showing no signs of cognitive decline. A case of a woman who at 78 years of age was diagnosed with partial trisomy excluding the APP region who died at the age of 83 showing no clinical symptoms of dementia or neuropathological lesions of AD has been reported (Prasher, 1998). Other reports mentioned in the literature include the cases of two women with 25% and 86% trisomy for chromosome 21 who at the ages of 83 and 74, respectively, showed no signs of clinical dementia (Chicoine and McGuire, 1997; W.B. Zigman, personal communication, 2000).

Biomarkers

β-Amyloid peptide levels

People with DS have higher plasma levels of soluble Aβeta peptide (Aβ) levels than individuals in the general population (Mehta et al., 1998).

Jones and colleagues (2009) reported no association between age and plasma Aβ 1–40 and plasma Aβ 1–42 concentrations, nor were plasma Aβ 1–40 and plasma Aβ 1–42 levels found to vary between people with DS with or without dementia. Matsuoka and colleagues (2009) have argued that it is the ratio of plasma Aβ 42/40 rather than absolute levels of the peptides that are important in contributing to the pathophysiology of AD.

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Changes in A β peptide levels with onset of AD and with the duration of dementia may account for a lack of difference between prevalent cases and individuals without dementia (Prasher et al., 2010).

Results from studies suggest that among adults with DS, decreasing levels of plasma A β_{42} , a decline in the A β_{42} /A β_{40} ratio, or increasing levels of A β_{40} may be sensitive indicators of conversion to AD, possibly reflecting compartmentalization of A β peptides in the brain (Schupf et al., 2010). A more recent investigation has shown that plasma A β levels are closely related to the presence of cerebral amyloid angiopathy, which is strongly associated with the development of dementia in DS (Head et al., 2017).

Telomere shortening

Telomeres, the repeated nucleotides that cap the ends of chromosomes, undergo shortening with each cell division, and therefore serve as markers of a cell's replicative history. Reduction in telomere length may be an indicator of cellular ageing and has been linked to AD in the general population (Panossian et al., 2003).

Jenkins and colleagues in 2006 reported shorter telomere length in T lymphocytes of individuals with DS and AD compared with age-matched paired individuals with DS without dementia. They have reported since then (Jenkins et al., 2010) that people with DS and mild cognitive impairment (MCI-DS) also have shorter telomeres than people with DS without MCI-DS. Furthermore, they demonstrated that light intensity measurements from chromosome 21 exhibited shorter telomeres in adults with DS with either dementia or MCI-DS compared to ageing per se. The authors suggested that chromosome 21 measurements appeared to be especially promising for use as a biomarker because of the lack of overlap in the distribution of telomere measurement scores between normal ageing, mild cognitive impairment, and dementia in individuals with DS. In a more recent study Jenkins and colleagues (2016) found consistent shortening of telomere length in five individuals with DS as they declined cognitively.

Neuroanatomical features in dementia

Neuropathology in ID

People with DS have smaller brains than individuals in the general population, and their brain size reduces with age and declines further with the onset of dementia (Schapiro et al., 1989). Macroscopic abnormalities in the brains of people with DS described in the literature have been summarized by Lubec and Engidawork (2002) as small, rounded, and foreshortened, with a steep rise of the occipital lobes and narrowing of the superior temporal gyri.

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The principal neuropathological features in AD dementia are the formation of senile amyloid plaques (SP) and neurofibrillary tangles (NFTs), AD neuropathology develops in many individuals with ID not due to DS. In a post-mortem series, Malamud (1972) reported no evidence of AD pathology among adults in this population for people under the age of 40 and a prevalence of 14% in individuals over 40 years old. Barcikowska and colleagues (1989) reported a prevalence of AD neuropathology in 31% in people with ID not due to DS who were over 65 years of age at the time of death.

Popovitch and colleagues (1990) examined the brains of 385 adults aged 23–90 years with ID without DS, metabolic disorder, or hydrocephalus. The presence of one or more NFTs and/or neuritic plaques (NP) was observed in 63.4% of all cases and varied with age. Recommended age-specific quantitative criteria for the diagnosis of AD (Khachaturian, 1985) were met in 9.5% of those cases below 50 years of age, 54.2% between 50 and 65, 70% between 66 and 75, and 87% of the cases greater than 75 years of age. However, in most cases the NP did not have a neuritic component containing paired helical filaments, and substantial numbers of NFT were seen in the frontal cortex, contrasting with results reported in the literature for the general population. The number of NP per square millimetre consistently increased with age for all areas examined, with the largest age-associated increases in density seen in frontal and temporal regions. In contrast, NFT density increased with age only within hippocampus and parahippocampal gyrus, but not in the neocortex.

In a study of similar individuals, Silverman and colleagues (1993) reported statistical independence of regional amyloid plaque and NFT densities although NP lesions within the neocortex were more diffusely distributed across regions for older cases compared to younger cases. Interestingly, no similar age-associated change in the topography of NFT was observed.

Neuropathology in DS

The majority of people with DS have senile plaques in their brains by the age of 40. However, the relationship between plaque count and dementia is poor; there is a much more robust correlation of the presence and severity of dementia with neurofibrillary tangle count (Margallo-Lana et al., 2007). Head and Lott (2004) suggest that there may be additional provocative factors in the development of dementia (e.g. apoE genotype, gender, individual differences in A β deposition) acting in parallel with compensatory events that would maintain brain function despite the accumulation of AD pathology. Such compensatory events reported in people with DS include neuronal growth response (spouting) in the hippocampus and frontal cortex at ages immediately before the development of full-blown AD pathology (Head et al., 2003, 2007; Ohara et al., 1999). This compensatory growth responses may occur in DS prior to extensive AD pathology and may be one mechanism underlying

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observations in PET studies of hypermetabolism in the entorhinal cortex of individuals with DS (Haier et al., 2003, 2008; Zigman and Lott, 2007).

In addition to the formation of SPs and NFTs there is evidence of cerebral amyloid angiopathy (CAA) in DS. This is because in DS there is overexpression of chromosome 21, leading to increased amyloid precursor protein (APP) production, which then leads to abnormal amyloid deposits. When the soluble protein tau is hyperphosphorylated the internal structure of the cell is deranged due to destabilization of microtubules; NFTs result, and cell death may occur. Enzymes such as dual specificity tyrosine-phosphorylation-regulated kinase 1A coded by *DYRK1a* gene and the DS critical region RCAN21 ('Regulator of Calcineurin') (Davies et al. 1998) are encoded on chromosome 21 and they play a role in tau formation. The pattern of NFT formation in DS follows the hierarchical pattern observed in AD (first layer II of the entorhinal cortex, followed by the hippocampus, and then the neocortex). SP deposition may commence in people with DS during adolescence, and NFTs appear later as the person ages (Mann and Esiri, 1989). It is the appearance of NFT deposits that induces AD symptoms despite the early presence of SP (Armstrong, 1994; Margallo-Lana et al., 2007).

Although Mann (2006) considers that the pathological changes that arise in DS and in AD are similar, later authors disagree (Nelson et al., 2011) and recent writers support the contention that the neuropathology of DS and AD are different (Ballard et al., 2016). It has been proposed that CAA should be increased in DS because the extra copy of APP leads to increased beta-amyloid peptide (A β) accumulation. CAA in DS was indeed found in significantly higher frequencies in brains of individuals with DS compared to sporadic AD and controls (Head et al., 2017). Hypertension and arteriosclerotic changes occurred commonly in those with sporadic AD whereas atherosclerosis and sclerosis of the smaller arterioles were rare in the cases with DS. The seminal role of A β accumulation in DS suggests a different mechanism of cell loss in this disease. This finding is supported by evidence that PET scanning of DS subjects has confirmed that amyloid deposition occurs before the onset of dementia and tau accumulation correlates with cognitive decline (Rafii et al., 2017; Fortea et al., 2020).

Other processes that may influence the development of dementia in DS are being investigated, in the search for new therapeutic interventions. Oxidative processes, mediated by mitochondria, may lead to protein damage and cognitive difficulties. Senile plaques and NFTs provoke an inflammatory response from microglia, which may lead to cellular damage. White matter changes have been reported in the younger adults with DS. White matter pathology may increase the risk of AD in non-DS individuals. Many of these processes are currently under investigation.

Neuroimaging

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Interested readers are referred to Beacher and Murphy (2006) and Schaer and Eliez (2007) for reviews on the subject. Compared with age matched non-ID controls without dementia, individuals with DS have a significantly greater age-related reduction in the volume of frontal, temporal and parietal lobes, and a significantly greater age-related increase in volume of peripheral cerebrospinal fluid (Beacher et al., 2010).

Brain computerized tomography scan studies on people with DS and dementia have reported changes similar to those seen in the general population with AD, including an increased degree of brain atrophy (Schapiro et al., 1992) and medial temporal atrophy (Ikeda and Arai, 2002). Studies using voxel-based morphometric (VBM) MRI scans (automated, observer-independent technique) of people with DS (White et al., 2003) support findings seen on volumetric MRI scans (Beacher et al., 2009). In a study of 27 people with DS without dementia (mean age 44.1 years) Teipel and colleagues (2004) found that the regional gray matter volume was decreased with advancing age in parietal, frontal, occipital, temporal, and parahippocampal regions. Gray matter volume was relatively preserved in subcortical nuclei, periventricular regions, the basal surface of the brain (bilateral orbitofrontal and anterior temporal areas) and the anterior cingulate gyrus. These findings suggest grey matter reductions in allocortex and association neocortex in the predementia stage of DS.

It is uncertain whether VBM offers a more accurate description of brain anatomy in DS than traditional techniques, as VBM includes statistical modelling assumptions that may not apply to populations known to have marked abnormalities in brain anatomy (Beacher and Murphy, 2006).

Functional neuroimaging using positron emission tomography (PET) measurements of fibrillar β amyloid ($A\beta$) burden and reductions in regional PET measurements of the cerebral metabolic rate for glucose (CMRgl) have been used in several studies in DS with and without dementia. People with DS and dementia have shown deficits in regional cerebral blood flow and glucose consumption, and regional pattern of fibrillary $A\beta$ deposition similar to that observed in late-onset AD and in additional frontal regions. (Sabbagh et al., 2015, 2011; Landt et al., 2011; Nelson et al., 2011).

Treatment

There is a lack of evidence for both pharmacological and psychological treatment of dementia in people with ID (Sheehan et al. 2015).

Pharmacological treatment: Cognitive enhancers

Despite a poor evidence base (Ballard et al., 2016) cholinesterase inhibitors are approved for the treatment of people with dementia in DS in the UK. The National Institute for Health and Care Excellence (NICE) has published a clinical evidence statement on pharmacological

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management of mental health problems in people with ID and dementia (NICE, 2016). They found that there was moderate quality evidence suggesting donepezil may be effective in treating cognitive decline and increasing adaptive behaviour in people with DS who do not yet have dementia (Kondoh et al., 2011; Prasher et al., 2002). There was little evidence supporting the use of memantine in the DS population (Boada et al., 2012; Hanney et al., 2012). A Cochrane review of the evidence was even less supportive, and Livingstone and colleagues (2015) concluded that, 'due to the low quality of the body of evidence, it is difficult to draw conclusions about the effectiveness of any pharmacological intervention for cognitive decline in people with DS'.

Other psychotropic medication

The use of psychotropic medication in people with ID and dementia should follow the same principles as those used in the general population, but with consideration that this group may be unusually sensitive to some medication as a result of reduced drug metabolism, reduced drug clearance, and reduced plasma protein binding. It is considered good practice when treating people with ID to start medication at a lower dose and to make increments at a lower rate than for the general population.

Depression is often associated with dementia in people with ID (Coppus et al., 2006). Selective serotonin reuptake inhibitors (SSRIs) are preferred in this population.

Sleep disturbance appears to be as common in people with ID and dementia (Espie, 2000) as in the general population with dementia (Vitiello and Borson, 2001). Some patients respond well to small doses of trazodone, despite the fact that this drug is not licensed for this indication. The dose ranges from 25 mg to 150 mg at night.

The drugs used for the treatment of epilepsy do not differ greatly from those used in younger people with ID. Sodium valproate is widely used, and the newer drug, levetiracetam, has benefits; senile myoclonic epilepsy in DS responds well to it (Aller-Alvarez et al., 2017; Vignoli et al., 2011). For the treatment of status epilepticus, NICE (2004) suggests the use of buccal midazolam, a short-acting benzodiazepine, at a dosage of 5–10 mg as an alternative to rectal diazepam. In people with DS, a lower dose of 2.5mg is preferable to avoid over-sedation. Buccal midazolam is unlicensed in the UK.

Psychological and psychosocial treatments

A mixture of nonspecific psychosocial interventions, such as reducing environmental demands, simplifying routines, and minimizing avoidable changes, would intuitively appear appropriate in the care of people with ID and dementia. Unfortunately, there are no studies evaluating the effectiveness of these interventions in people with ID and dementia (Royal College of Psychiatrists and British Psychological Society, 2015). If problem behaviours arise in the course of dementia in ID guidance is

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given on assessment and intervention (Royal College of Psychiatrists, 2007).

Practical considerations

To move or not to move

Janicki and Dalton (1998) argued that, wherever possible, people with ID and dementia should stay in their usual place of residence, 'dying in place', with the necessary adaptations to meet the person's increasing health needs, including provision of palliative care (Thompson and Wright, 2001). If this is not possible, then they should be transferred to a residence within an ID service, 'referral in', with the last preferred option being a 'referral out' of ID services when the person is transferred to services for older people. However, persons with ID may have been placed in a residence when they were young without considering their long-term needs. Not uncommonly, these placements cannot be adapted to suit the requirements of a person with dementia. Given the lack of provision of specialist placements for people with dementia within ID services, many of these people end up on an emergency placement or in a general nursing home.

Compared with older people with ID not due to DS, ageing adults with DS encounter more relocations, and are more likely to have their final placement for end-of-life care in a nursing home (Patti et al., 2010)

End-of-life decisions

End-of-life decisions are made in between one quarter and one half of people with ID (Lohiya et al., 2002; Wagemans et al., 2010). This figure is similar in those of normal intelligence (van der Maas, 1997). The prevalence and nature of end-of-life decisions was investigated in a Dutch study of medical files of people with ID who died between January 2002 and July 2007 (Wagemans et al., 2010). The authors found that one or more end-of-life decisions were taken in over half of the deaths in that period, but the family had been involved in decision-making in only half of the cases. They also found no information in the medical notes about the process of end-of-life planning and no evidence that any of the people with ID were consulted in taking an end-of-life decision. The wishes of people with ID are often unknown because of lack of mental capacity. In these cases, a decision should be made according to what others consider are the best interests of the person (Mental Capacity Act, Department for Constitutional Affairs, 2005). It is recommended that a formal discussion involving carers, the GP, family, and advocates, should take place to determine what are thought to be the best interests of the person before the person with ID dies (Lohiya et al., 2002).

The Department of Health (2008) End of Life Strategy provides best-practice examples for management of people with ID and dementia towards the end of their lives. Recently the International Summit on Intellectual Disability and Dementia produced a report (Watchman et al.,

2017) on end-of-life care in advanced dementia. The report recommended that palliative care providers should be informed about such cases and adults with ID should be consulted early on in their advance care planning (McCallion et al., 2017).

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Sleep and circadian rhythm disorders

Chapter: Sleep and circadian rhythm disorders

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Introduction

The importance of enquiring about sleep patterns was recognized by Hippocrates as early as 400 BCE when he wrote 'sleep and watchfulness, both of them when immoderate, constitute disease'. Unfortunately, many medical students and doctors-in-training receive little or no training in sleep medicine (Stores, 2007). Sleep disorders, remain largely unrecognized, under-diagnosed, and under-treated (Stores, 2007, Rosenberg, 2015).

This vital physiological process occupies a third of our adult lives and disrupted sleep has immediate and long-term consequences on physical and mental health. For the old age psychiatrist, two of the most important functions of sleep remain regulation of normal affect and normal

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cognition—not only just simple attention and vigilance, but also the key role of memory consolidation and new learning (Cellini, 2017).

There is also emerging evidence that sleep, acting via the glymphatic system, is vital for the clearance of toxic protein aggregates from the brain (Tarasoff-Conway et al., 2015). In humans, disruption of slow-wave sleep has been shown to increase cerebrospinal fluid (CSF) antibody levels (Ju et al., 2017), providing support for the hypothesis that sleep disruption may perpetuate the neurodegenerative cascade (Wu and Swaab, 2007).

Primary sleep disorders are common with the prevalence of these disorders increasing with age. These include sleep related breathing disorders, restless legs syndrome (RLS), periodic limb movements of sleep (PLMS), circadian rhythm disorders, and parasomnias such as REM sleep behaviour disorder (RBD). Sleep disturbance may also be a result of medical and psychiatric comorbidities, as well as polypharmacy.

Sleep disturbance commonly occurs in psychiatric disorders and is often regarded as a secondary phenomenon that will improve following treatment of the underlying psychiatric disorder. Insomnia has been shown to be a risk factor for subsequent development of depression (Pigeon et al., 2017). There is often a tendency to attribute sleep disturbance in those with mental health problems to the psychiatric diagnosis or the psychotropic medication, rather than as a distinct and treatable set of disorders.

Sleep disturbance is common in patients with dementia, with a prevalence of 24.5% reported in a sample of patients with mild to moderate Alzheimer's disease (AD) (Moran et al., 2005). In neurodegenerative disorders, the development of a significant sleep disturbance is often the reason for a patient to enter residential care (Pollak and Perlick, 1991; Bianchetti et al., 1995). The association between sleep and dementia is bidirectional: abnormal amyloid and tau deposition may affect the structure and functioning of brain networks mediating sleep (Ju et al., 2014; Holth et al., 2017) and impair the production and release of melatonin (Ju et al., 2014); and sleep disturbances may perpetuate the neurodegenerative cascade (Wu and Swaab, 2007). However, treatment of sleep disorders in the field of dementia remain challenging: hypnotic medications are commonly used, but evidence for efficacy is lacking and limited by side effects (Forlenza et al., 2017). Melatonin and nonpharmacological interventions like light therapy have not yet demonstrated efficiency in clinical trials (Kinnunen et al., 2017). Nursing homes pose a particular challenge for sleep: limited daytime sunlight exposure, night-time noise, nursing practices, and low physical activity also contribute to sleep disruption.

This chapter provides the tools to identify and treat patients presenting with signs or symptoms associated with poor sleep.

Sleep and circadian rhythm disorders

The anatomy and neurochemistry of sleep and wakefulness

The control of sleep and wakefulness is a complex process that involves an interplay between various brain regions and neurotransmitter systems. Sleep is controlled by two distinct but overlapping neuronal circuits (Borbely, 1987; Borbely, 1982; Daan et al., 1984). The homeostat drives an increasing pressure to sleep after every hour awake and the circadian rhythm drives alertness in the day and sleep at night (Borbely & Achermann 1999; Borbely et al., 2016). Once a threshold in the pressure to sleep is achieved that is appropriate for the phase in the circadian rhythm, sleep ensues (Fig. 48.1).

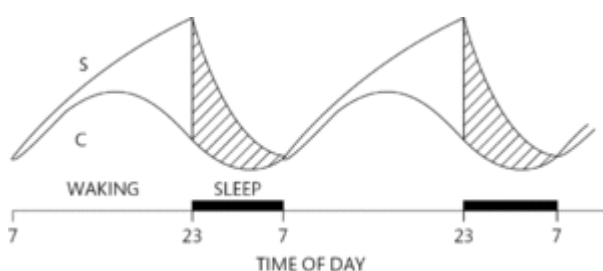


Fig. 48.1

The two-process sleep model. Process S represents the homeostatic process to sleep, which increases with the duration of time spent awake. Process C represents the circadian rhythm. The two processes interact to determine the gating of sleep: the greater the difference between Process S and Process C, the higher the sleep pressure, which is typically when sleep ensues.

Adapted with permission from Borbély, A.A., et al. The two-process model of sleep regulation: a reappraisal. *Two-Process model*, 25(2): 131-143. Copyright © 2016 European Sleep Research Society. <https://doi.org/10.1111/jsr.12371>.

The neural circuits mediating sleep remain far from being completely understood but can be grouped into four systems: the wakefulness-promoting system, the non-REM sleep promoting system, the REM sleep promoting system, and the hypocretin/orexin system which maintains wakefulness and suppresses REM sleep. These systems interact with the circadian pacemaker located within the suprachiasmatic nucleus (SCN) and a sleep homeostatic system. Readers are referred to these excellent reviews written on this subject (Scammell et al., 2017; Saper and Fuller, 2017; Weber and Dan, 2016).

Circadian rhythm generator

The internal circadian clock is highly conserved throughout evolution and modulates all cellular processes, physiology, and behaviour, including the sleep-wake cycle (Bell-Pedersen et al., 2005). The SCN is the site of the internal clock and coordinates and regulates a network of cellular clocks

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throughout the body (Mohawk et al., 2012). The SCN itself keeps time via a group of 'clock genes', which also serve as transcription factors for other genes, thereby influencing physiological processes (Duffield, 2003; Wilking et al., 2013).

The most powerful timekeeper or 'zeitgeber' to regulate the SCN is light intensity which is detected via the intrinsically photosensitive retinal ganglion cell (ipRGC) containing the photopigment melanopsin. These cells have direct projections to the SCN and the intergeniculate leaflet via the retinohypothalamic tract and optic tract respectively. The SCN then makes further connections to the ventrolateral preoptic nucleus (VLPO) and the pineal gland.

In humans, blue light is particularly effective at activating the melanopsin photopigment and thereby suppressing melatonin production. Photo-entrainment of the circadian rhythms thus occurs: with sunlight exposure suppressing melatonin release and darkness promoting melatonin release. Other than light, other physiological signals also act as 'zeitgebers' or timekeepers including physical activity, temperature, and body position.

Wakefulness-promoting systems

The wakefulness-promoting system includes the cholinergic cell groups located at the basal forebrain, parabrachial nucleus, pedunculo pontine and laterodorsal tegmental nuclei, and the monoaminergic regions (locus coeruleus, dorsal and median raphe, ventral tegmental area, and tuberomammillary nucleus), which produce noradrenaline, serotonin, dopamine, and histamine, respectively. These are collectively termed as the ascending reticular system and project to the thalamus and throughout the cortex to cause wakefulness.

NREM sleep-promoting systems

The NREM sleep-promoting systems include the GABAergic and galanin secreting cell groups (ventrolateral preoptic area, median preoptic nucleus, basal forebrain, parabrachial nucleus), which inhibit the wake-promoting neurons in the caudal hypothalamus and the brainstem, and project widely to the cortex to promote sleep.

REM sleep-promoting systems

The pons is the site of REM sleep generation. The cholinergic pedunculo pontine and laterodorsal tegmental nuclei (collectively known as REM-on nuclei) project to the REM-off nuclei in the brainstem. Glutamatergic neurons located in the sublaterodorsal nucleus produce muscle atonia by exciting GABAergic/glycinergic neurons in the ventromedial medulla and spinal cord that in turn hyperpolarize motor neurons.

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The hypocretin/orexin system

Hypocretin 1 and 2, which are also known as orexin A and B, are neuropeptides secreted from the lateral hypothalamus. In the 'flip-flop switch model', hypocretin has been proposed to act to by stabilizing sleep-wake transitions (Saper et al., 2001, 2005).

Influence of psychotropic medications on sleep and sleep disorders

The major neurotransmitter systems, involved in the maintenance and wakefulness and sleep and the medications exerting therapeutic and side effects on these systems are as summarized in Table 48.1.

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Table 48.1 Major neurotransmitter systems involved in the maintenance of wakefulness and sleep, and drugs exerting therapeutic and side effects on these systems.

Major nuclei	Histamine TMN	Serotonin Raphe nucleus	NA Locus coeruleus	Dopamine Mesencepha lon, substantia nigra pars compacta	ACh LDT-PPT, nucleus Meynert	Glutamate Reticular formation	GABA VLPO	Melatonin Pineal gland
Function	Arousal system (via hypothalamus forebrain)				Thalamocorti cal arousal system		Sleep induction	Circadian rhythms
Wakefulness	+++	+++	+++	+++	+++	+++	0	0
Slow wave sleep	+	+	+		+	+	+++	+++
REM sleep	0	0	0		+++	0	+++	+++
Agonist drugs	Low-dose doxepin	SSRI, SNRI e.g. venlafaxine		Amphetamine , L-dopa, dopamine agonists, methylphenid ate	ChEI		Benzodiazepi ne, Z- hypnotics (nonbenzodia zepines), ethanol	Melatonin ramelteon agomelatine

Sleep and circadian rhythm disorders

Antagonist drugs	Antihistamines Pitolisant (inverse agonist)		Prazosin	Neuroleptics	Scopolamine, atropine, TCA	Ketamine, memantine	Flumazenil	

ACh, Acetylcholine; 5-HT, 5-hydroxytryptamine; GABA, gamma-aminobutyric acid; NA, noradrenaline; TMN, tuberomammillary nuclei; LDT-PPT, laterodorsal tegmental and pedunculopontine tegmental nuclei; VLPO, ventrolateral preoptic area; SSRI, selective serotonin reuptake inhibitors; ChEI, cholinesterase inhibitors; REM, rapid eye movement sleep; SNRI, Serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressants.

+++ , high activity; ++ , intermediate activity; + , low activity; 0 , no activity.

Sleep and circadian rhythm disorders

Psychotropic medications with their broad range of effects on various CNS neurotransmitters can commonly cause either insomnia or daytime sedation as common side effects (Doghramji and Jangro, 2016).

Antidepressants modulate various monoamine transmitters and also interact with histamine and muscarinic cholinergic receptors. Depending on their specific pharmacological profile, antidepressants have differential effects on sleep. Selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs) and the activating tricyclic antidepressants all tend to cause deterioration in sleep quality. SSRIs commonly cause treatment-related insomnia at initiation. (Thompson, 2002) The sedating antidepressants, trazodone and mirtazapine, decrease sleep latency and increase slow-wave sleep due to their antagonistic action on the 5HT₂ receptors; with mirtazapine having additional H₁ receptor antagonism. The tertiary amine tricyclic antidepressants (e.g. amitriptyline) tend to cause sedation, whereas the secondary amine tricyclic antidepressants (nortriptyline) tend to be more activating. Doxepin is a highly selective H₁ antagonist with effective sedation with fewer side effects compared to other tricyclic antidepressants and it has been approved by the FDA for the treatment of insomnia.

Wakefulness and the sleep stages

The different stages of sleep and wakefulness are defined by specific electroencephalogram (EEG), electro-oculogram (EOG) and electromyogram (EMG) features on polysomnography, such that we are either awake or alternate between non-rapid eye movement (NREM) or rapid eye movement sleep (REM) at approximately 90–120-minute cycles (Fig. 48.2). NREM sleep is further subdivided into light NREM sleep (N1 and N2) and deep NREM sleep (N3) which is also termed as slow-wave sleep. Sleep stages are scored according to standardized criteria (Berry et al., 2015).

Sleep and circadian rhythm disorders

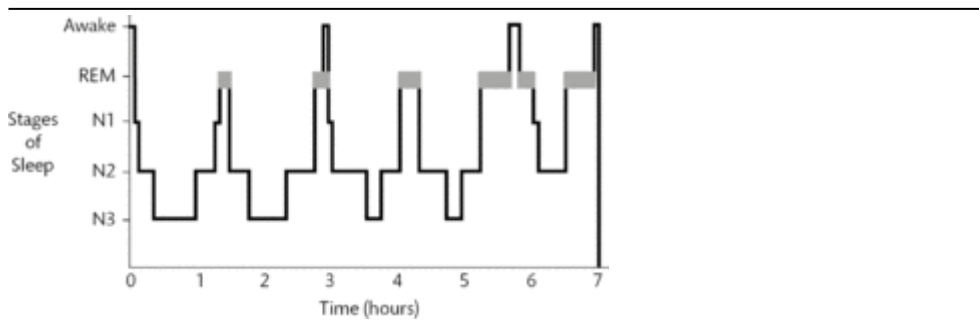


Fig. 48.2

The sleep hypnogram. The sleep hypnogram in a young adult: sleep stages over a typical night as determined by polysomnography. During adult life, at night we cycle between non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep approximately every 90–120 minutes. REM sleep typically occurs > 90 minutes into the night and NREM sleep is divided into three stages; N1, N2, and N3. N3 is often known as slow wave sleep (SWS). The normal young adult will wake two to four times during the night although may not be aware of this. Most adults will have four to five cycles of REM sleep, although dream recall is highly variable and few patients recall four to five distinct cycles of dreaming. Age-related physiological changes in the sleep architecture that are typically observed in older compared to younger adults include: delayed time to sleep onset, fragmented sleep with frequent awakenings, and early morning awakenings with decreased time spent in the deeper stages of sleep.

During wakefulness, the EEG typically shows low-amplitude and high-frequency activity predominantly in the alpha range (7–14Hz) with a variable amount of muscle activity detected on EMG.

NREM sleep is characterized by slower EEG frequencies in the delta (0–4Hz) and theta (4–7Hz) ranges with decreases in muscle tone. N1 sleep is a brief transition state characterized by drowsiness and slow rolling eye movements. N2 sleep is characterized by the presence of sleep spindles and K complexes. N3 sleep is dominated by high-amplitude delta activity.

REM sleep is associated with most of our emotional dream content and has EEG appearances similar to that of the awake state with additional theta activity. Complete paralysis of postural muscle activity occurs. During REM sleep, rapid bursts of fast saccadic eye movements occur.

Sleep stages normally transition from N1, N2, to N3 sleep, followed by a period of REM sleep before cycling back to NREM sleep 4–6 times during a night. Through the course of the night, REM sleep episodes become longer.

Sleep and circadian rhythm disorders

Numerous physiological changes in sleep occur as part of normal ageing. Total sleep time decreases: younger people average 8.9 hours of sleep which decreases to an average of 7.4 hours in older people (Klerman and Dijk, 2008). Sleep architecture is altered with an increased proportion of time spent in the lighter stages of sleep. There is also increasing sleep fragmentation and increased time to fall asleep in healthy older adults with and without sleep complaints (Gooneratne and Vitiello, 2014), with a tendency to phase advance by 30 minutes earlier a decade from the third decade onwards (Skeldon et al., 2016). Daytime napping, night-time arousals, and recalled awakenings become more common. Ageing is associated with an increase in apnoea-hypopnoea index (AHI) and decreases in oxygen saturation (Moraes et al., 2014). However, it is important to recognize that, although normal ageing results in changes in sleep, this should be distinguished from sleep complaints, which are indicative of an underlying sleep disorder.

Current classification of sleep disorders

Sleep disorders are classified into one or more of four categories: hypersomnia, insomnia, circadian rhythm disorder, and parasomnia. Common evening and night time disorders also include restless legs syndrome (RLS) and associated periodic limb movements of sleep (PLMS).

The most recent International Classification of Sleep Disorder, 3rd Edition (ICSD-3) was revised in 2014 and has been used for the diagnostic criteria discussed here (Medicine, 2014). DSM-5 diagnostic classifications have been listed where relevant.

How to assess a patient for a sleep problem—taking a sleep history

Given the value placed on the history taking within psychiatry, a sleep history should be routine. Many sleep disorders can be accurately diagnosed by history alone.

Simple screening questions will often help to identify the type of sleep problem with which you are dealing (see Box 48.1 for a suggested proforma). Thereafter, specific sleep problems are best characterized by a more thorough history if needed. A collateral history from the bed partner is very helpful to determine the presence of snoring or breathing abnormalities, the characteristic pattern of periodic limb movements of sleep, sleepwalking, or other parasomnia. It is important to ask about the duration and course of symptoms.

Box 48.1 Recommended questions for a sleep history

Sleep and circadian rhythm disorders

1. Do you snore heavily? Has anyone witnessed prolonged pauses in breathing (apnoeas)?

For typical obstructive sleep apnoea the snoring is very loud, often heard outside the bedroom door, sometimes by neighbours, the pauses are typically 20–30 seconds rather than brief <5–10 seconds, a snort or a start at the end of apnoea is characteristic.

2. Do you have unpleasant tingling or discomfort in the legs, which makes you need to kick or to move? Is it worse in the evenings, is it helped by moving? (restless in the body rather than a racing mind)

Everybody needs to be asked specifically about restless legs as people can find it hard to describe the dysaesthesia 'wriggly, itchy, worms under the skin'. Bed partners can be asked about the infuriatingly regular kicks that may wake them but not the patient—every 20–30 seconds is typical.

3. What drugs do you take and when do you take them?

Including the dose and timing of caffeine/alcohol and nicotine. Consider over the counter medication that might affect sleep.

Short-acting painkillers, sedative opiates, adrenergic drugs that exacerbate insomnia such as inhalers or some nasal sprays, counting the cups of coffee or tea, are all important.

4. Take me through your typical 24 hours—describing the sleep/wake pattern over a day.

Particularly helpful for those with sleep restriction, circadian rhythm disorder, and insomnia.

5. Do you nap during the day—if so, when, and for how long?

Can you get through the day without sleeping and examples of when they might sleep can help to distinguish fatigue from true hypersomnia, few of us would sleep in the middle of a conversation or with food in our mouths.

6. Do you have any history of nightmares, acting out of dreams, sleepwalking out of the bedroom? If so, at what time of night do things tend to happen?

Typically, the first cycle of REM sleep starts 90 minutes into the night, so REM parasomnias are more likely in the second half of the night. NREM parasomnias can occur within the first hour of sleep.

Comorbid medical or psychiatric disorders and the occurrence of chronic pain should be noted, and their relationship with the onset of the sleep problem should be explored. A list of prescribed and over-the-counter medications, as well as the timing of medications should be obtained.

Sleep and circadian rhythm disorders

Patients may develop sleep-related side effects as a result of not taking medications at the prescribed timings. In the elderly with unexplained sleepiness, special attention should be paid to nocturia as it could be the only clue to previously undiagnosed obstructive sleep apnoea.

Discussing the patient's expectations of normal sleep is a fundamental part of treatment in insomnia disorder. For those with significant daytime sleepiness, driving safety should be discussed. The American Academy of Sleep Medicine (AASM) recommend asking 'have you had crashes, near misses or claims on insurance in the last year?'; people who are aware of nodding off at the wheel or have modified driving behaviour have been shown to be at higher risk of accidents (Ghosh et al., 2012).

To further assess a patient's sleep, one of the simplest and cost-effective diagnostic test is a sleep diary kept for at least two weeks. Fig. **48.3** shows two examples of sleep diaries.

Sleep and circadian rhythm disorders

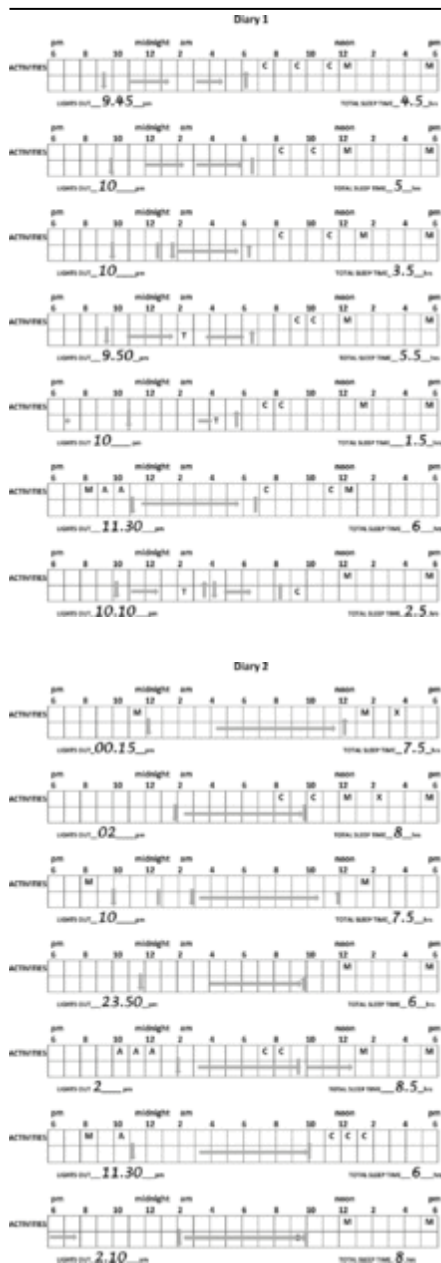


Fig. 48.3

Sleep and circadian rhythm disorders

Sleep diaries. The patient should be instructed to complete the diary once a day, typically in the morning and think about their best estimate of the night. Lights out, lights on, and night-time awakenings should be noted. Any daytime naps should be noted and their estimate of total sleep time in hours. Daytime activities such as meals, exercise, caffeine intake, and alcohol consumption can be noted in some diaries. Ideally the diary should be completed for two weeks. Diary 1. Insomnia disorder where time in bed is far longer than time perceived asleep, both difficulty initiating and maintaining sleep is seen without day time naps. The variability among nights is seen with occasional good nights of prolonged sleep. Diary 2. Delayed sleep phase syndrome in a 23-year-old male who had this sleep pattern since the age of 15. Despite getting into bed early, the pattern is of falling asleep typically between 2.30am and 4am but waking well after 11am with few night awakenings. The estimated total sleep time is far greater than for the patient with insomnia.

There has been a dramatic increase in the use of commercial accelerometers as lifestyle gadgets. As of 2016, more than 80 sleep-tracking apps and sensors were available on the market of which only a small number have since been approved by the US Food and Drug Administration (FDA) or recommended by the NHS Apps Library (Shelgikar et al., 2016). Overall, these devices lack standardization and generally underestimate waking and overestimate sleep efficiency compared to conventional polysomnography (Shelgikar et al., 2016). Paradoxically, the frequent checking of such devices can exacerbate insomnia. However, voice recorder or smart phone video data which can capture sleeptalking, parasomnia, or snoring can be helpful.

Screening questionnaires—which scales to use?

The Epworth Sleepiness Scale (ESS) is a widely used validated questionnaire to assess daytime sleepiness as self-rated over the prior month (Johns, 1991). Patients are asked to estimate their chances of actually dozing or napping in a series of listed situations. Advantages of the score include speed and simplicity for the patient. Critics point out that it correlates poorly with more objective measures of sleep in the laboratory (Fong et al., 2005) and does not predict driving safety. The normal range within the original study was 4–9, and many people with typical insomnia score 0 or 1, while a score of over 10 is taken as daytime sleepiness. One advantage of the score is to then assess any subsequent intervention for sleepiness.

Another widely used screening tool is the Pittsburgh Sleep Quality Inventory (Buysse et al., 1989). Seven questions ask about time in bed, time taken to fall asleep, and satisfaction with sleep. The scoring system gives a single score with above 5 indicating some form of sleep disturbance and people scoring above 10 having more severe sleep disturbance.

Sleep and circadian rhythm disorders

The Insomnia Severity Index is quick and easy to complete, and it is more often used to assess both severity and improvement after therapy with scores ranging from 0–24 (Bastien et al., 2001).

Insomnia disorder

Insomnia disorder is defined as difficulty falling asleep, difficulty staying asleep, and subsequent daytime distress and impaired functioning.

Earlier diagnostic criteria for insomnia emphasized a distinction between ‘primary’ and ‘secondary’ insomnia. With the increasing recognition that medical and psychiatric disorders are often comorbid (Ohayon, 2002; Riemann, 2007), the most recently revised ICD-10 and DSM-5 diagnostic criteria for insomnia have now merged these previously distinct diagnostic entities into the single entity of Insomnia Disorder.

Numerous epidemiological studies have shown an association between reduced sleep duration with adverse medical and psychiatric outcomes: including a greater risk of cardiovascular disease (Gami et al., 2013; Sabanayagam and Shankar, 2010; Ayas et al., 2003) and increased risk of the subsequent development of depression (Baglioni et al., 2011; Ellis et al., 2014).

Insomnia remains the commonest sleep disorder in primary care, with at least 10% of the population affected (Morin et al., 2006). Increasing age is a risk factor for insomnia due to both accumulating comorbidities as well as age-related physiological changes in sleep.

Assessment

The diagnosis is typically made on the basis of the history, alongside sleep diaries. It is important to exclude common mimics. Typically, ESSs are low, in the range of 0–2. High ESSs should prompt screening for other secondary causes of insomnia. In older patients, at least 10% will have RLS and 20% will have obstructive sleep apnoea (OSA).

Polysomnography is generally unhelpful unless a secondary cause of insomnia is suspected such as OSA. It is surprisingly difficult to distinguish between isolated insomnia disorder and insomnia disorder with comorbid OSA (Lichstein et al., 2013). Another common mimic is circadian rhythm disorder, where patients perceive difficulty initiating sleep with delayed sleep phase, but in fact then stay asleep well.

The cornerstone of both diagnosis and therapy is recording of sleep diaries, where a typical pattern of far more time in bed awake than asleep is usually seen. The sleep efficiency (total sleep time/time in bed) can be calculated. Normal sleep typically has a sleep efficiency of over 85%, whereas patients with severe insomnia often have sleep efficiency less than 50%. Fatigue rather than daytime sleepiness is usually described. A hypervigilant phenotype is typical with a description of a ‘racing mind’ that finds it hard to switch off. A common model of causation includes:

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predisposing factors; a precipitating trigger; and subsequent perpetuating or maladaptive behaviours that worsen rather than improve sleep and disrupt both the normal homeostatic and circadian drivers to sleep (Spielman et al., 1987).

The history should include questions about the typical 24-hour pattern but also about the environment and bedroom itself. Review of the prescription list for all potentially stimulant medications is required, and an assessment of mood is also needed. It is common to hear the patient catastrophize about the impact of poor sleep upon work and driving, but there is often a mismatch between perceived performance and more objective assessments. The prior and current use of sleeping tablets needs to be documented as these in themselves can be contributing to some of the daytime fatigue.

Treatment of insomnia

Although newer pharmacological therapies with more specific mechanisms of action have been developed, the recently published guidelines by the European Sleep Research Society (ESRS), American College of Physicians, and AASM have again emphasized the role of cognitive behaviour therapy for insomnia (CBTi) as the first line treatment for insomnia where available, with pharmacological therapies considered only as second line treatments (Riemann et al., 2017, Qaseem et al., 2016, Sateia et al., 2017). These guidelines are broadly aligned in their recommendations. Recommendations from the European guidelines for the pharmacological treatment of insomnia are presented in Box 48.2 (Riemann et al., 2017)

Cognitive behavioural therapy

CBTi has been shown to be an effective treatment for older patients as well as patients with other comorbidities. Obviously, the presence of significant cognitive impairment precludes the use of CBTi and pharmacological therapies are typically used instead. CBTi has been shown in randomized control trials to result in sustained benefits and was superior to benzodiazepine therapy when assessed 6–12 months after treatment discontinuation (Mitchell et al., 2012; Morin et al., 2009). The more widespread use of CBTi has been limited by the lack of local service provision. However, recent studies on internet-based CBTi have been promising, showing similar efficacy to traditional forms of CBTi (Zachariae et al., 2016; Seyffert et al., 2016).

CBTi is a set of techniques that strengthen the bed–sleep association, realign the homeostatic mechanisms and circadian rhythm, and decrease anxiety and rumination about sleep. Sleep hygiene measures represent only part of the techniques used in CBTi, and their use in isolation is ineffective for the treatment of insomnia (Morgenthaler et al., 2006). CBTi would typically include: sleep hygiene, sleep restriction, stimulus control, cognitive therapy and relaxation therapy. Exercise was not

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emphasized in the original CBTi regimes, although recent research has highlighted its positive impact on sleep (Chennaoui et al., 2015).

Sleep restriction is the cornerstone of treatment in CBTi. Using a sleep diary, the average sleep duration is obtained, which is then used to restrict the time that the patient can spend in bed in order to achieve a high sleep efficiency. Patients are instructed to maintain strict schedules to wake up at the same time throughout the week. The time permitted in bed is then progressively increased.

Pharmacological treatments

Pharmacological therapies are recommended as second line therapy for the treatment of Insomnia Disorder (Riemann et al., 2017; Qaseem et al., 2016). In the elderly population, the risk-benefit ratio should be carefully considered (Schroeck et al., 2016). Major drug classes used to treat insomnia include the benzodiazepines, non-benzodiazepine receptor agonists ('Z-drugs'), antidepressants, antipsychotics, antihistamines, and phytotherapeutics, as well as the newer drugs such as melatonin receptor agonists and orexin receptor antagonists. The evidence for the use of these medications for the treatment of insomnia has been reviewed by the ESRS and the AASM (Riemann et al., 2017; Sateia et al., 2017). Despite recent excitement over the availability of agents with more selective modes of action, the evidence of long-term benefit for these therapies remains weak. There is a marked disparity between the number of medications obtaining FDA approval and those recommended for use by the AASM (Sateia et al., 2017).

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Box 48.2 Pharmacological therapies recommended for the treatment of insomnia

Recommended drug classes for the short-term (≤ 4 weeks) treatment of insomnia when CBT-I is not effective or not available:

- Benzodiazepines
- Non-benzodiazepine receptor agonists
- Sedating antidepressants

Drug classes NOT recommended for the treatment of insomnia:

- Antihistamines
- Antipsychotics
- Melatonin
- Phytotherapy
- Valerian
- Other complementary therapies

Source: data from Riemann, D., Baglioni, C., Bassetti, C. et al. 2017. European guideline for the diagnosis and treatment of insomnia. *Journal of Sleep Research*, 26(6): 675–700.

At present, hypnotics are approved for only for short-term (two to four weeks) treatment of insomnia. Benzodiazepine use is still common in the elderly population (Olfson et al., 2015). Use of benzodiazepines in the older population is associated with confusion, psychomotor impairment, falls, and daytime fatigue (Glass et al., 2005). Although improvements in sleep quality, total sleeping time, and reduced arousal are observed, the overall risks often outweigh the benefits (Glass et al., 2005). A meta-analysis of 45 randomized clinical trials showed that benzodiazepine use reduced sleep onset latency by just over four minutes (Holbrook et al., 2000). Furthermore, the placebo effect of medications in insomnia trials cannot be ignored (Winkler and Rief, 2015). There is a widely held perception among physicians that intermittent prescription of hypnotics reduces side effects but this view is not supported by any randomized controlled trials.

Benzodiazepines act via binding to the gamma-aminobutyric acid (GABA) receptors. The choice of benzodiazepine depends on their different pharmacokinetics: drugs with a short half-life are used to treat sleep onset insomnia, and drugs with a longer half-life are used to treat sleep maintenance insomnia (Schroek et al., 2016).

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The non-benzodiazepine receptor agonists ('Z-drugs') were developed with the aim of avoiding the side effects of benzodiazepines and act by binding more selectively to the GABA(A) receptor alpha 1 subunits. Although they have a better safety profile, observational studies have shown that they are associated with adverse cognitive outcomes, sleep walking, fractures, and serious injury (Schroek et al., 2016).

Sedating antidepressants have weak evidence for benefit, with tolerance developing quickly: low-dose doxepin is recommended only for sleep maintenance and trazodone is not recommended by the American Guidelines (Sateia et al., 2017). However, trazodone, which lacks anticholinergic activity and has a more favourable side effect profile compared to benzodiazepines, has been useful in community-dwelling patients with AD (Camargos et al., 2014). Doxepin is used more commonly as an anti-insomnia drug in the US. At low doses, doxepin has high affinity for the histamine H1 receptors with few side effects, so it could be useful in older people (Krystal et al., 2010). However, clinical effects are mainly on sleep maintenance and not sleep initiation (Yeung et al., 2015).

Antihistamines and antipsychotics are not recommended for the treatment of insomnia (Riemann et al., 2017; Sateia et al., 2017).

Melatonin acts on the melatonin receptors, which are highly expressed in the suprachiasmatic nucleus. Newer drugs acting on this pathway include ramelteon (Kato et al., 2005), a MT1/MT2 melatonin receptor agonist, and agomelatine. Melatonin and ramelteon have been shown to reduce sleep onset latency. However, their overall benefits are modest and the evidence for their use in insomnia is limited (Riemann et al., 2017). In the American Guidelines, ramelteon has a short half-life and is recommended for sleep onset insomnia but there is no convincing role for melatonin (Sateia et al., 2017).

Suvorexant, a reversible antagonist at the orexin receptors A and B, has been recently licensed for use in the US. Benefits so far have been modest, with a meta-analysis showing that it resulted in a modest decrease in sleep latency by 6.4 minutes (Kuriyama and Tabata, 2017). It has only been recommended for the treatment of sleep maintenance insomnia in the American Guidelines (Sateia et al., 2017).

Sleep-related breathing disorders

The sleep-disordered breathing (SDB) disorders include OSA, central sleep apnoea (CSA), sleep-related hypoventilation disorders, and sleep-related hypoxemia disorder.

A diagnosis of SDB is made when more than five apnoeas or hypopnoeas are present per hour of sleep (AHI >5 events/hour). The diagnosis of OSA and CSA is then made depending whether the majority of events are classified as obstructive or central.

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Obstructive sleep apnoea

OSA is by far the most common cause of significant daytime sleepiness in individuals over the age of 50. Unfortunately, the disorder is often overlooked despite having an excellent therapy with continuous positive airways pressure (CPAP) (McDaid et al., 2009).

Untreated OSA is associated with significant morbidity and mortality. Severe OSA is associated with hypertension, atherosclerosis, atrial fibrillation, and an increased risk of stroke (Lavie et al., 2000; Zhou et al., 2017; Wang et al., 2013; Zhang et al., 2015). Epidemiological studies suggest that the presence of SDB is associated with an increased risk of developing subsequent cognitive impairment (Leng et al., 2017), and could potentially be a modifiable risk factor for dementia (Liguori et al., 2017).

The biggest risk factors are male sex and increasing age. At particular risk are those over the age of 50 with obesity and increased neck circumference (>17 inches). In the Wisconsin Sleep Study Cohort, mild OSA (AHI >5) was present in 43% of men and 28% of women aged 50–70 years of age, with moderate to severe OSA in 17% of men and 9% of women. (Peppard et al., 2013). In institutionalized patients with dementia, the reported prevalence of OSA is extremely high, with 70% meeting the diagnostic criteria for mild OSA, and almost half the cohort having severe OSA with an AHI ≥ 20 (Ancoli-Israel et al., 1991).

Psychiatry patients have particular risk factors for sleep apnoea with reported higher rates of 20–50% (Benca et al., 1992; Anderson et al., 2012). Variable ascertainment and selection bias make interpretation of such studies challenging but there is most evidence for increased rates in major depressive disorder and in those with elevated body mass index (BMI) (Gupta and Simpson, 2015).

Assessment

History from the bed partner is helpful. Spouses are often aware of loud snoring and pauses in breathing. It is rare for the patient themselves to be aware of the apnoeas or to have a perception of choking. Although snoring is common in OSA, snoring in itself is not specific for the diagnosis.

The typical OSA history includes progressively troublesome sleepiness and awaking unrefreshed. Mild morning headache is common. Clues for those who live alone include a dry, sore throat in the morning, nocturia, awaking unrefreshed, vivid dreams, and night-time sweating alongside daytime sleepiness.

The clinical presentation of OSA in the older patient can be atypical. It is important to recognize that at least 20% of patients with OSA are not overweight. Compared to younger patients with similar disease severity, older patients with SDB tend to have a lower BMI and neck

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circumference (Chung et al., 2009). Although excessive daytime sleepiness (EDS) is frequently reported, a significant proportion of patients with OSA do not have EDS. There is an age-related reduction between SDB and the symptoms of sleepiness, with older patients reporting a lesser severity of sleepiness compared to younger patients with similar disease severity (Morrell et al., 2012). Neuropsychiatric symptoms, including cognitive impairment and affective disorders, can be a presenting feature of OSA. On polysomnography, age-related increases in AHI and decreases in oxygen saturation occur. For example, in one study in a large population-based sample, average AHI in individuals aged 55–59 ranged from 11.1 ± 14.2 ; increasing to 21.9 ± 20.5 in individuals aged 75–80 (Moraes et al., 2014). Mild SDB is common in the older people, and it remains unclear whether elderly patients without significant symptoms require treatment.

Nocturia is a common geriatric syndrome traditionally regarded as a symptom of lower urinary tract disorders, but the diverse aetiology including that of sleep disorders is now recognized (Dani et al., 2016). In elderly patients with unexplained sleepiness and no other medical comorbidities to cause nocturia, attention should be paid to nocturia itself, which may sometimes be the only clinical clue to previously undiagnosed OSA.

It is also worth mentioning chronic fatigue syndrome, which is a diagnosis of exclusion. Sleep disorders must be excluded prior to the diagnosis and OSA is a common mimic (Gotts et al., 2013, Mariman et al., 2013).

The STOPBang is a particularly helpful short screening tool for those at high risk of OSA (Chung et al., 2008). Higher scores in the range of 5–8 have a high sensitivity of over 90% for moderate OSA, and low scores in the range of less than 3 have a high negative predictive value for OSA. The ESS is also helpful as a measure of baseline functional impairment and to assess treatment response.

People with suspected OSA should be referred for further investigations and typically within the UK this would involve a domiciliary sleep study, which measures a limited number of parameters, including airflow, nasal pressure, respiratory effort, ECG, and oxygen saturation, rather than in-patient polysomnography. An AHI score of over 5 is regarded as abnormal, but if it is greater than 15 (moderate) or 30 (severe) then symptomatic sleepiness is far more likely to occur.

Treatment

CPAP is first line therapy for the treatment of OSA. Other lifestyle changes that should be instituted include weight loss, avoidance of alcohol and other sedatives, and adopting non-supine sleep positions. Weight loss on its own can result in improvements of OSA severity; however, improvement to normal levels of AHI (<5) only occurs in a minority of patients.

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CPAP acts as a pneumatic splint to keep the oropharynx open. CPAP therapy significantly improves quality of life, daytime sleepiness, mood, and cognitive impairment. Improving sleep probably has an impact upon affective disorders, although further large RCTs are needed to demonstrate this robustly (Wells et al., 2007).

In older patients with OSA, CPAP results in beneficial effects on cardiovascular mortality, stroke incidence, and stroke mortality (McMillan and Morrell, 2016). CPAP adherence is not affected by advancing age. Even in patients with AD, adherence to CPAP treatment can be achieved (Ayalon et al., 2006) and treatment may slow down cognitive decline in AD (Troussiere et al., 2014).

Alternative treatments to CPAP include (Lorenzi-Filho et al., 2017): oral appliances that advance the mandible, upper airway stimulation of the hypoglossal nerve, nasal expiratory positive airway pressure (EPAP), the Winx device (a mouthpiece sited within the oral cavity and connected to an external console to generate a negative pressure), and oropharyngeal exercises. These alternative therapies are less effective, but may be useful in patients who cannot tolerate CPAP.

Symptomatic OSA is notifiable to the driving licence authorities but patients typically can restart driving when compliant with treatment.

Central sleep apnoea

CSA refers to repeated pauses in both respiratory effort and airflow during sleep. This can result either from ventilatory instability or depression of brainstem respiratory centres or chemoreceptors.

In older people, CSA is encountered in the presence of heart failure, prior stroke, neurodegeneration, and use of sedative medications, in particular opiates and hypnotics. Chronic opioid use places individuals at a greater risk of developing CSA, and to a lesser extent, OSA (Filiatrault et al., 2016). Relevant studies have suggested that the prevalence of sleep disordered breathing could be as high as 70–85% in patients taking opioids (Mogri et al., 2008; Correa et al., 2015).

People taking over 200mg of morphine or an equivalent dose are at the greatest risk, in particular if this is in combination with benzodiazepines. While people with chronic pain typically complain of bad sleep, this is mostly attributed to the pain itself, rather than considering apnoeas secondary to opioid use as a possible cause.

Assessment

Unlike patients with OSA, many with CSA do not complain of EDS. To diagnose CSA, a respiratory sleep study or polysomnography is necessary to demonstrate the lack of ventilatory effort that characterizes this disorder.

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Treatment

There are currently no evidence-based treatments for the management of CSA in patients with heart failure (Khayat and Abraham, 2016). Recent interest in the potential role of adaptive servo-ventilation (ASV) has declined with the publication of a large randomized control trial that showed that treatment resulted in increased cardiovascular mortality (Cowie et al., 2016). There is some limited evidence for benefit in opioid-induced CSA but cessation of medication is clearly the best option if possible (Van Ryswyk and Antic, 2016).

Circadian rhythm disorders

There are six distinct circadian rhythm disorders currently defined by ICSD-3. The circadian rhythm disorders are caused by misalignment of the period of sleep and they are characterized by a relatively normal length of sleep time and quality of sleep but occurring out of step with societal norms.

These disorders include:

- Advance sleep-wake phase syndrome
- Delayed sleep-wake phase syndrome
- Irregular sleep-wake rhythm disorder
- Shift work disorder
- Jet lag circadian rhythm disorder
- Non-24 sleep-wake syndrome

There is an increasing recognition of the relatively high frequency of circadian rhythm disorders occurring in psychiatric patients (Abbott et al., 2015), with a delayed sleep-wake phase syndrome and non-24-hour sleep-wake syndrome in particular being associated with psychiatric comorbidity (Reid et al., 2012). Of the circadian rhythm disorders, the advanced sleep-wake phase syndrome and irregular sleep-wake syndrome are most commonly encountered by old age psychiatrists.

Assessment

The diagnosis of the various circadian rhythm disorders relies principally on the clinical history where the bedtime, falling asleep, and wake times are determined. In advanced neurodegenerative disease, a caregiver history is often helpful.

Actigraphy and sleep diaries are helpful for confirming the diagnosis and determining the optimal timing of melatonin treatment if required.

Advanced sleep-wake phase syndrome

The circadian rhythm tends to advance with increasing age, with the advanced sleep-wake phase syndrome being probably the most common

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circadian rhythm disorder in older adults (Martin et al., 2006). Although psychiatric comorbidity is less common in advanced sleep-wake phase syndrome than in the delayed sleep-wake phase syndrome, a careful history should allow the early morning awakenings of advanced sleep-wake phase syndrome to be distinguished from early morning awakenings typical of major depressive disorders.

Patients typically fall asleep from 6 to 9pm, with a normal duration of six to eight hours of sleep before awakening in the early morning between 2 and 5am.

Treatment

The AASM 2015 clinical practice guidelines recommends treatment with bright light therapy in the evenings for the treatment of advanced sleep-wake phase syndrome (Auger et al., 2015).

Delayed sleep-wake phase syndrome

It is rare for the isolated delayed sleep-wake phase syndrome to present late in life, hence restless legs, depression, or chronic insomnia should be excluded. The disorder typically presents in teenage years with patients who fall asleep and wake far later than the societal norm, causing associated daytime dysfunction. The diagnosis can be made on the history alone, alongside well completed sleep diaries (Fig. 48.3, see Diary 2). For many the key question is 'if you were allowed to sleep when you wanted, would you sleep well?' The quality of sleep is typically good but patients tend to fall asleep between 3 and 4 am and then struggle to wake in the morning. Those woken early may have daytime sleepiness.

Treatment

In older patients where there is no societal pressure to wake at fixed times for work, treatment may not be required.

The AASM 2015 clinical practice guidelines recommend precisely timed melatonin in adult patients with delayed sleep-wake phase syndrome (Auger et al., 2015). Melatonin in conjunction with bright light therapy delivered one hour prior to the habitual waking time may be more effective than either therapy alone (Burke et al., 2013). Chronotherapy, whereby the sleeping time is advanced further until the desired sleeping time is achieved, may be helpful in highly motivated patients.

Irregular sleep-wake rhythm disorder

Irregular sleep-wake rhythm disorder is characterized by the loss of a distinctive sleep-wake pattern and is commonly encountered in schizophrenia, neurodegenerative disorders and institutionalized patients. Caregivers typically report frequent daytime napping, and patients may complain of either night-time insomnia or EDS. Sleep and

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wake episodes are fragmented across the 24-hour cycle. However, the total sleep time may be normal for age.

Treatment

Clinical practice guidelines from the AASM recommend the use of light therapy in elderly patients with dementia with irregular sleep wake rhythm disorder (Auger et al., 2015). In institutional settings, 'mixed modality treatment', which consists of various interventions including: keeping individuals out of the bed during the daytime, light daytime physical activity, morning bright light exposure, a structured bedtime routine, and minimization of night time noise, has been shown to result in decreases in daytime sleep and improvements in night time sleep. Melatonin has not shown to be of benefit, and the use of other sleep-promoting agents is discouraged (Auger et al., 2015).

Excessive daytime sleepiness or hypersomnia

Hypersomnia affects up to 15% of the adult population with around 5% severely affected and describing functional impairment (Ohayon et al., 2002).

The differential diagnoses of EDS are wide. Potential causes of EDS include:

- Too little sleep (e.g. sleep restriction)
- Poor-quality sleep (e.g. sleep apnoea, restless legs, external triggers)
- Hypersomnia (e.g. medication, medical comorbidities, narcolepsy, idiopathic hypersomnia)
- Circadian rhythm disorder (e.g. shift work (>40), delayed sleep phase (teens and 20s))

As mentioned previously, obstructive sleep apnoea is a common diagnosis in older people, with a new diagnosis of narcolepsy and idiopathic hypersomnia being far less common. EDS might be attributable to previous head trauma: this is most commonly transient for the first three to six months after injury but, if it persists, other causes should be screened for (Gardani et al., 2015).

The cause of hypersomnolence tends to be multifactorial in older patients as a result of neurodegenerative disorders (Bhat and Chokroverty, 2017), comorbid medical and psychiatric disorders, sleep disturbances, and medication side effects.

In patients with psychiatric comorbidities, hypersomnolence is common, particularly in major depressive disorders, and it can be difficult to reliably differentiate hypersomnolence resulting from the underlying psychiatric disorder from the side effects of medications or hypersomnolence related to other causes. Barateau and colleagues (2017)

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provide a helpful diagnostic and treatment algorithm in the evaluation of hypersomnia in this patient population.

Assessment

The diagnosis is based on a detailed sleep history and completion of sleep diaries, including information on the episodes of subjective sleepiness, number and duration of naps, and episodes of 'sleep attacks'. The ESS is helpful to determine the severity of sleepiness. Objective measures such as actigraphy can be useful in institutionalized individuals.

In older patients, a full polysomnography is recommended to exclude other sleep disorders and also to document an adequate duration of sleep prior to the performance of the Multiple Sleep Latency Test, which can identify sleep-onset rapid eye movements and short sleep latencies. The Maintenance of Wakefulness Test can be used to monitor treatment.

Treatment

Treatment of hypersomnia is focused on treatment of the underlying cause. Behavioural measures such as a structured schedule with fixed bed and wake times, regular exercise, restriction of daytime naps, and bright light exposure are helpful in improving sleep.

Although there are a number of different alerting agents such as modafinil, armodafinil, dexamphetamine, and methylphenidate available for the treatment of hypersomnia (Takenoshita and Nishino, 2017), concerns about cardiovascular risk, drug interactions, and abuse potential limit the use of these medications, particularly in older people.

Parasomnias: 'things that go bump in the night'

Described as 'undesirable physical and/or experiential phenomena accompanying sleep,' parasomnias can involve complex and occasionally prolonged motor acts, such as walking, eating, texting, and even driving a car. Parasomnias are broadly divided into those occurring in NREM sleep and those occurring in REM sleep.

Parasomnias are common in psychiatric disorders, with reported prevalences reaching almost 40% for nightmares, 20% for sleep paralysis, and 10% for sleep-related eating disorders and sleepwalking (Waters et al., 2017). REM sleep behaviour disorder (RBD) typically manifests in the older population and is the focus of this section.

REM sleep behaviour disorder (RBD)

In normal REM sleep, a powerful, descending, glutaminergic signal from the brainstem inhibits the spinal motor neurons, resulting in muscle atonia (Luppi et al., 2013). In RBD, a progressive degeneration of this inhibitory brainstem control results in the loss of normal REM atonia, resulting in dream enactment behaviour alongside vivid and often violent dream content. Behaviours commonly observed include shouting, kicking,

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and punching. Events are typically violent, but a range of milder behaviours are also recognized (Rodriguez et al., 2017). RBD typically occurs in the second half of the night. Up to 70% of patients will cause injury to themselves or their bed partner.

The condition predominantly affects older men with a reported prevalence of at least 1% (Chiu et al., 2000, Kang et al., 2013). RBD was first described in 1986 in a small series of elderly men (Schenck et al., 1986). In fact, there were reports of selective brain stem lesions in cats causing oneiric or dreamlike behaviours in animal models as long ago as 1967 (Mouret et al., 1967).

RBD is traditionally classified into idiopathic or secondary forms. Secondary RBD can be caused by a neurodegenerative disorder, particularly the synucleinopathies; a structural lesion; antidepressants, in particular the SSRIs and SNRIs (Lee et al., 2016, McCarter et al., 2015); beta-blockers; and alcohol withdrawal. Discontinuation of the antidepressant may result in clinical and polysomnographic resolution of RBD. However, RBD has also been reported to persist and antidepressants may simply unmask individuals with a latent neurodegeneration.

There is increasing debate whether true idiopathic RBD exists with an increasing recognition of the strong association between RBD and the subsequent development of neurodegenerative disease, particularly the synucleinopathies, such as Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy, with 91% developing one of these conditions over 14 years of follow up (Iranzo et al., 2013).

Assessment

The diagnosis of probable RBD can be made with a positive history of dream enactment or complex motor behaviours occurring from sleep. Patients are often unaware of these behaviours unless injury has occurred, so therefore a collateral history is essential. In RBD, it is typical to obtain a history of the behaviours beginning insidiously and infrequently as limb jerks and sleep talking before progressing to become nightly or near nightly violent events.

A number of validated screening questionnaires are available to help make a diagnosis of probable RBD. However, these questionnaires are unable to distinguish RBD from other NREM parasomnias, sleep apnoea, and nocturnal confusion. Occasionally, severe OSA can cause strikingly vivid dreams and agitated arousals termed as 'pseudo-RBD', hence a diagnostic polysomnography should be performed in patients who have other features to suggest OSA. To make a definite diagnosis of RBD, polysomnography is required to identify the excessive EMG activity that occurs in REM sleep (REM sleep without atonia, RSWA; see Fig. **48.4**).

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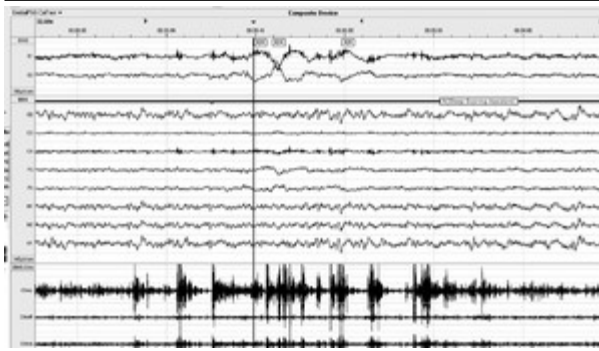


Fig. 48.4

In-patient video polysomnography in a patient with REM sleep behaviour disorder. In this in-patient video polysomnography, eye movements in the two electro-oculogram traces (E1, E2) are displayed in the two top traces where large amplitude rapid eye movements characteristic of REM sleep are observed. Electroencephalography (EEG) traces are displayed in the next eight traces (O2, C3, C4, F3, F4, M1, M2, and O2), which show low-voltage desynchronized EEG activity that is observed in REM sleep. Chin movements are displayed in the bottom three chin EMG traces (ChinL, ChinR, and ChinA). In normal REM sleep, REM atonia occurs and the Chin EMG activity should be reduced. However, in this patient with REM sleep behaviour disorder (RBD), phasic bursts of increased muscle activity are seen during REM sleep. This is abnormal and reflects the loss of normal REM atonia in RBD.

Treatment

There is debate as to how and when patients with idiopathic RBD should be counselled on their future risk of developing a neurodegenerative disorder, but many patients are aware of associations with RBD so this is often part of the consultation.

Behavioural interventions to ensure a safe sleeping environment should be implemented to prevent injury to the patient or their bed partner. If comorbid OSA is present, treatment of OSA often improves RBD. Medications known to exacerbate RBD should be discontinued where possible.

There are no licensed therapies for RBD but clonazepam has been regarded as the first line treatment for RBD. It has no effect on RSWA but usually suppresses RBD behaviours in most patients. A lack of response should prompt the clinician to re-evaluate the diagnosis of RBD. The use of clonazepam is contraindicated in comorbid OSA. Common side effects, including sedation, falls, confusion, cognitive impairment, and respiratory depression, often limit dose escalation and so this drug should be used cautiously (Anderson and Shneerson, 2009).

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Melatonin has been used as a second-line therapy and demonstrated effectiveness when evaluated in one small randomized blinded cross-over trial (Kunz and Mahlberg, 2010). Unlike clonazepam, melatonin is able to restore normal REM atonia. Melatonin also tends to be better tolerated with a better adverse effect profile than clonazepam, with similar efficacy although there are no head-to-head trials (McCarter et al., 2013). The effective dose range is 2-12mg, with a recent large case series showing benefit at an average of 6mg (McCarter et al., 2013). Other recently developed melatonin receptor agonists such as ramelteon and agomelatine have only been studied in small numbers of patients with inconsistent results so far (Jung and St Louis, 2016).

In patients for whom RBD remains refractory, occasional case reports have described that rivastigmine and sodium oxybate may be effective (Di Giacopo et al., 2012; Moghadam et al., 2017).

Sleep-related movement disorders: restless legs syndrome and periodic limb movements of sleep

RLS is underdiagnosed in older patients. The disorder is characterized by an urge to move the body in order to relieve uncomfortable sensations that typically occur in the legs. The urge to move is prominent during periods of inactivity and tends to be worse in the evenings. Symptoms can be episodic or wax and wane, and not all patients have sleep disturbance. However, people with moderate or severe symptoms may have considerable sleep disturbance.

RLS has a female predominance (Berger et al., 2004). The prevalence ranges from approximately 4-15% and is more common in the Caucasian population. At least 50% will have a family history. In older people, estimates of the prevalence of RLS have ranged from 6 to 37% (Beaulieu-Bonneau and Hudon, 2009; Guarnieri et al., 2012). Late onset RLS (defined as onset >45 years) tends to have a more rapid onset and progression to a continuous syndrome (Allen and Earley, 1996).

Although several studies have suggested that RLS could be associated with a wide variety of medical disorders, in fact only end-stage renal disease and iron deficiency have a strong association with RLS (Trenkwalder et al., 2016). High caffeine intake, smoking, excess alcohol, and exercise close to bed time can exacerbate RLS. Comorbid depression and anxiety are common in RLS (Mackie and Winkelman, 2015). Several psychotropic medications exacerbate symptoms, particularly those that deplete dopamine as well as some antidepressants and melatonin. Among antidepressants, mirtazapine, SSRIs, and SNRIs are more likely to worsen RLS, whereas bupropion and sedative antidepressants such as trazodone and doxepin do not have this effect (Kolla et al., 2017; Mackie and Winkelman, 2015).

PLMS is a closely related disorder whereby involuntary limb movements occur during wake or sleep but typically in the first half of the night. They

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overlap with RLS but can be an isolated phenomenon. Patients (or a frustrated bed partner) can describe these strikingly periodic limb movements which typically consist of a brief, triple flexion movement of the toe, foot, and ankle with an interval of 20–30 seconds before the next movement occurs. PLMS are present in 80% of patients with RLS (Montplaisir et al., 1997), but are not specific and can be found in other conditions.

Assessment

The diagnosis of RLS is based on the clinical history. Patients can find it difficult to describe the sensations, and often use terms such as ‘creeping, itchy, fidgety, crawling’. The discomfort is felt deep within the limbs. Pacing and walking are seen in more severe cases. Other parts of the body can be affected, such as the back and less commonly the arms. Unlike people affected by the pain of arthritis or peripheral neuropathy, those with RLS are better or symptom free when walking.

Many disorders are commonly confused for RLS: these include neuropathy, akathisia, myalgia, venous stasis, leg oedema, arthritis, leg cramps, positional discomfort, and habitual leg tapping. Excluding these disorders is now formally incorporated as one of the five mandatory diagnostic criteria for RLS (Allen et al., 2014).

Ferritin levels should be checked in all patients, as values below 75ng/ml are often associated with RLS.

Further tests to confirm the diagnosis include using polysomnography to record the typical periodic limb movements with both limb EMG and video. This also helps to exclude other or additional causes of sleep disturbance, such as OSA. Some units have access to lower limb foot actigraphy that can be used over two or three nights at home to record a periodic limb movement index.

Treatment

Drug treatment should be initiated only when symptoms interfere with sleep, quality of life, and functioning. In patients with low levels of ferritin (<75ng/ml), iron replacement can improve symptoms.

Nonpharmacological interventions include sleep hygiene measures and avoidance of caffeine and nicotine close to bedtime.

Until recently, low-dose dopamine agonists were used as the first-line treatment of RLS, and ropinirole, pramipexole, and the rotigotine patch are all licensed for use. Treatment is typically very effective, but augmentation can occur in up to 60% of patients (Silver et al., 2011, Lipford and Silber, 2012), in which patients develop earlier onset and increased severity of symptoms over time. Impulse control disorders also develop in a significant minority.

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Recent guidelines published by the IRLSSG/EURLSSG/RLSF have now recommended that the alpha-2-delta ligands (gabapentin enacarbil, gabapentin, and pregabalin) should be used as the first-line therapy (Garcia-Borreguero et al., 2016).

In the situation where dopaminergic therapies are still required for symptom control, only the lowest possible dose for the shortest duration should be used.

As dopamine agonists are associated with the development of impulse control disorders, these should be actively screened for.

Conclusions

Sleep changes with age, but sleep disorders cannot be considered to be part of normal ageing. They are commonly associated with mental or physical disorders, pain, and neurodegenerative disease. Polypharmacy can further contribute to sleep problems. An in-depth clinical history is the key to diagnosis. Sleep disorders are under-recognized and nonpharmacological treatment strategies are underused. Patients need to be informed about the physiological changes of sleep with normal ageing and the principles of sleep hygiene, such as more physical activity and less napping during daytime, and the restriction of alcohol, coffee, and nicotine in the evening hours. The most common sleep disorders in older age are insomnia, obstructive sleep apnoea, RLS, and REM sleep behaviour disorder. Most management strategies include pharmacological and nonpharmacological treatment strategies.

Additional helpful information can be found in comprehensive textbooks for sleep medicine (Kryger, 2010; Chokroverty, 2017) or on the websites of the World Federation of Sleep Research and Sleep Medicine Societies (<http://www.wfsrms.org>), which also include links to other national organizations such as the AASM (<http://www.aasmnet.org>).

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The effects of ageing on personality

Chapter: The effects of ageing on personality

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Introduction

In the twenty-first century, mental health can no longer simply be viewed as the *absence* of mental illness. In later life, and indeed across the lifespan, the aim of the commissioners of mental health services is to enhance wellbeing and quality of life as well as to promote good mental health (e.g. Age Concern England, 2006). For clinicians working directly with older people, the question may often arise as to the extent to which the older person's current state of wellbeing (or ill-being) reflects more the person's life-long attitudes, coping style, and personality, rather than the current circumstances and context.

Such questions are fuelled by research demonstrating that there is in fact a *positive* relationship between increasing age and subjective wellbeing, despite the influence of apparent 'risk factors' in older age such as bereavement, ill-health, etc., which would be expected to have a cumulative negative effect on wellbeing. Many older people encounter

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difficult life circumstances in later life; how is it that most older people maintain or improve wellbeing when life appears to be so difficult? For example, Siedlecki and colleagues (2008) examined factors associated with wellbeing in 818 people aged from 18 to 94. Wellbeing was greatest in the oldest age group, and was predicted by personality factors such as neuroticism, not by health status. This stability of wellbeing in the face of accumulating adversity has been termed the 'wellbeing paradox' (Staudinger, 2000) or the 'satisfaction paradox' (Diener et al., 1999) and the consistent identification of this across many studies, populations, and measures suggests that it is probably not simply a methodological artefact.

This chapter examines the interactive effects of personality and ageing. Although the title of the chapter may suggest a one-way direction of influence of ageing on personality, it is now recognized that personality characteristics may provide a valuable resource, with a demonstrable impact on outcomes in health and wellbeing. This chapter explores the role of personality and the self as a source of psychological resilience in relation to ageing and wellbeing. It describes how the self is able to maintain continuity and stability and to change adaptively. Diener and colleagues (1999) suggest that the maintenance of wellbeing across the life span demonstrates the ability of the person to adapt positively to a wide range of conditions, highlighting the role of the individual in achieving a sense of wellbeing in older age. We thus discuss a dynamic interaction between personality and ageing, which must also take into account that 'ageing' itself is not a unitary process, but covers a range of influences that change, often variably, over time.

The chapter also considers whether personality does change as people age, or whether it remains stable across the lifespan. According to Allemand and colleagues (2007, pp. 323-4), 'many people have the impression that older adults are, in general, more rigid, stubborn, resigned, and conscientious than younger adults.' Of course, such stereotypes may confound differences between birth cohorts with the effects of the passage of time. Early theories, developed from the perspective of psychoanalysis, provided detailed accounts of personality development during childhood and adolescence, but did not appear to conceive that personality could continue to develop during adulthood and accordingly had nothing to say about personality development in older age. More recent approaches suggest that personality can show elements of both change and consistency across the life course. This chapter presents some of the theory and research relating to personality and ageing. It considers personality as a range of traits and resources, i.e. the characteristics or qualities within the individual that predispose the person to behave in characteristic ways across a range of situations. Knowledge of a person's personality profile helps to predict how the person will behave in any given situation, but there will, of course, be many other factors that influence the interaction between person and environment. Staudinger (2015) describes the multidimensional nature of

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ageing: 'human development and aging are the result of the continuous interaction between biological influences, sociocultural influences, and the decisions and competencies as well as beliefs and attributions of the developing individual himself or herself' (p. 188).

As cognitive impairment and dementia are seen as a particular challenge to adaptation in older people, the chapter concludes with reference to the impact of dementia on personality and, likewise, the impact of personality on the presentation of the person with dementia.

Personality across the lifespan

The 'Big Five' five-factor model has emerged as the predominant trait model of personality (Digman, 1990), and has been described as offering a meta-theoretical framework of personality (McCrae and Costa, 1996). The five factors included in this model are:

1. Neuroticism, including anxiety and vulnerability vs emotional stability
2. Extraversion, including warmth, gregariousness and activity vs introversion
3. Openness to experience, including broad-minded values and aesthetics
4. Agreeableness, including altruism, modesty, and trust vs ruthless and hostile
5. Conscientiousness, including competence, goal-directedness, self-discipline, and self-control

These factors form a crucial part of the self-concept. With its origins in psychometrics and the study of individual differences, the five-factor model represents a scientific approach to the study of personality. It is derived from factor analyses of descriptions of personality that were obtained through self-report methods and observer ratings that have been extensively validated. Each trait represents a tendency to behave in a particular way, with individuals varying in the extent to which they show each trait. It is the consensus on this model that has underpinned the revival of research on personality development over the lifespan.

Based on evidence from longitudinal and cross-sectional research, using a personality measure that evaluates these five traits (the NEO-PI), it had been previously argued that there is little or no change in personality after the age of 30, despite the varied experiences that occur over the life course (Costa and McCrae, 1992; 1994; 1997). 'Individual differences in personality traits are extremely stable in adults, even over periods of as long as three decades' (McCrae, 2002, p. 309). A longitudinal study, with 684 participants aged 17–76 undertaking three personality assessments over a period averaging 20 years, concluded that 'personality stability plateaus early in adulthood' (Terracciano et al., 2010). Such findings have been related to the proposition that personality traits are biologically determined, with environmental and secular influences seen as less

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important. An alternative, less-researched, view highlights plasticity in personality, as in other areas of development, reflecting the potential for age-related changes to be modified (Staudinger, 2015). In considering personality stability and change, it is important to note that there are at least three forms of stability that are being discussed: changes in the absolute *level* of scores; changes in the *rank order* of individuals (consistency); and changes in the *structure* of personality (Staudinger, 2005).

The *structure* of the five-factor model does appear to be replicable across age-groups (Allemand et al., 2007) with similar age-trends identified across diverse cultures. McCrae and colleagues (2005) used observer ratings of personality across 50 different cultures. The raters were college students and those being rated were college age (18–21) or adult (40–98); however, the mean age of the adult group was relatively young at 49.9 years. They found that the five-factor model of personality was consistent cross-culturally, providing further support for the argument that personality development is independent of life experiences.

Similarly, the evidence for stability of *rank order* of individuals is relatively strong in mid-life. Roberts and DelVecchio (2000) conducted a meta-analysis of relevant studies, indicating that stability plateaued in the 50–73-year-old age group, but it is noteworthy that there were no studies included with age groups older than this. Subsequent studies including older people in their samples have produced mixed results. Mottus and colleagues (2012) concluded there was rank order stability on the five factors in longitudinal analyses of two cohorts, one aged 69 initially, followed for three years; the other aged 81 initially and reassessed six years later. Lucas and Donnellan (2011) report analyses of a large German longitudinal sample, including over 9,000 adults aged 49–84, indicating lower rank order stability in the older groups for all five of the NEO traits. Specht and colleagues (2011) report analyses from the same study, replicating an inverted U-shaped curve for rank order stability, with the peak between the ages of 40 and 60, for all the traits except conscientiousness, the stability of which continued to increase with age. Similar findings of lower stability in later life are reported from samples in New Zealand (Milojev and Sibley, 2017) and Australia (Wortman et al., 2012), but with different traits showing higher stability (agreeableness in New Zealand; extraversion and conscientiousness in Australia).

Greater variation in later life is a classic gerontological finding, with heterogeneity typically attributed to the wide range and increasing diversity of life events experienced across the life span. For example, Allemand and colleagues (2013) state ‘individual differences in change reflect the plurality and diversity of life experiences individuals can encounter in adulthood such as getting married or getting fired from job, retirement, or physical and cognitive decline in later adulthood.’ Terracciano and colleagues (2018) have identified a potential major influence on the reductions in rank order stability noted in most, but not all, studies involving older people. They analysed data from nearly 10,000

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people, aged 50–96, assessed twice, with a four-year interval, on the Big Five personality traits. The results indicated once again that there was a progressive reduction in rank order stability with advancing age. However, when the results for those with cognitive impairment and dementia were analysed separately, it was evident that stability was especially low in this group, perhaps reflecting personality changes in dementia discussed later in this chapter. Among those without cognitive impairment or dementia, there was no evidence of lowered rank order stability with age. They conclude that the observed lower rank order stability of personality traits with increasing age is attributable to cognitive impairment and dementia, not age per se.

There is a large body of evidence that indicates that changes in mean *levels* of personality traits may occur beyond the age of 30 (Roberts et al., 2006). Here we focus on changes in later life, where data are now available from several large-scale studies, incorporating both cross-sectional and longitudinal analyses.

Extraversion

Almost all studies show a reduction with age in extraversion, especially in older cohorts (e.g. Specht et al., 2011; Lucas and Donnellan, 2011; Wortman et al., 2012; Kandler et al., 2015) and towards the end of life (Wagner et al., 2016). In a sample aged 80 and over, Berg and Johansson (2014) reported that this decline was related to hearing impairment. Where longitudinal studies have shown increases in extraversion, this has been with younger samples (aged 60–69) and/or over shorter periods. For example, Mottus and colleagues (2012) report decreased extraversion over a six-year period in a cohort initially aged 81, but a small increase in a younger cohort (aged initially 69) over a briefer, three-year period.

Agreeableness

Across the life span, large cross-sectional studies indicate higher levels of agreeableness in mid- and later life (e.g. Donnellan and Lucas, 2008). However, longitudinal analyses in later life generally show a reduction in agreeableness over time (Specht et al., 2011; Lucas and Donnellan, 2011; Wortman et al., 2012). Mottus and colleagues (2012) report a gender difference, with decreased agreeableness over time in females (but not males) in both their young-old and old-old cohorts.

Conscientiousness

In cross-sectional analyses, this trait increases from adolescence, before plateauing around the age of 50 or so (Donnellan and Lucas, 2008), with some studies showing older cohorts having higher levels still (e.g. Specht et al., 2011; Wortman et al., 2012). However, most longitudinal analyses in later life show reduced conscientiousness over time (Specht et al., 2011; Lucas and Donnellan, 2011; Wortman et al., 2012; Mottus et al., 2012; Kandler et al., 2015).

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Neuroticism

Donnellan and Lucas (2008) report discrepant age trends from two large cross-sectional samples. In a UK sample, consistent with other findings, neuroticism decreased with age; in Germany, it appeared to increase. Longitudinal analyses also produce mixed results; decreases in neuroticism are most often reported (e.g. Allemand et al., 2007; Allemand et al., 2008; Wortman et al., 2012; Mueller et al., 2016; Milojev and Sibley, 2017). However, Kandler and colleagues (2015) report increased neuroticism over time and Wagner et al. (2016) report increased neuroticism especially towards the end of life.

Openness

There appears to be a reduction in openness in later life, after a period of stability in mid-life (Donnellan and Lucas, 2008). This pattern is supported by most longitudinal analyses (Specht et al., 2011; Lucas and Donnellan, 2011; Mottus et al., 2012; Wortman et al., 2012). Wagner and colleagues (2016) report openness decreasing over time or towards the end of life.

Other triggers

Despite many differences between studies in samples and methods, there do appear to be distinct normative changes in personality beyond the original age of 30 previously suggested by Costa and McCrae, demonstrating that there is no specific age at which personality traits stop changing—development continues. In later life, reductions in absolute levels of extraversion, openness, and conscientiousness may be observed. Although agreeableness may be higher than in younger cohorts, it too may reduce over time. Neuroticism generally—but not in every sample—appears lower in later life.

In contrast to the notion that personality is biologically determined, Roberts and colleagues (2006) argue that, across the lifespan, some of the changes between and within cohorts could be affected by aspects of the environment. This is supported by Specht and colleagues (2011), who suggest changes in old age were partly attributable to social demands and experiences, and by Kandler and colleagues (2015), who relate individual differences in change to environmental sources, indicating plasticity in later life. This plasticity is evident in studies where an increase in openness in older people has been identified following cognitive training interventions (Jackson et al., 2012; Staudinger, 2015).

Wrzus and Roberts (2017) have proposed the 'TESSERA' framework, where personality development arises from processes of association and reflection concerning repeated short-term sequences of Triggering situations, Expectancies, States/State Expressions, and ReActions. Triggers might occur resulting from social, environmental, or health-related losses, with heterogeneity occurring as individuals experience these triggers at different times, or not at all. They suggest that further

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diversity results from less fixed social role expectations in later life, and from cognitive impairment affecting the reflective and associative processes that ultimately drive personality change.

Other factors may also lead to differences; for example, Allemand and colleagues (2008) suggest that reductions in neuroticism in later life may reflect a survivor effect, with those lower in neuroticism perhaps living longer. The changing context of later life is also likely to be an influence. Billstedt and colleagues (2013) demonstrate a clear cohort effect, comparing the scores of people aged 75 and over on the Eysenck Personality Inventory in 1976–1977 with those of people of the same age in 2005–2006. They report an increase in extraversion and a reduction in social desirability bias, suggesting a more independent-minded, outward-looking cohort than 30 years previously. Neuroticism levels, on the other hand, did not differ between the cohorts, presumably less influenced by the environmental and social context.

In summary, there is increasing acceptance that both change and stability in personality occur in later life (Allemand et al., 2013), and there is clearly a need to recognize the interaction of genetic and environmental influences. Measures of personality traits are, of course, designed to show stability, so considering other aspects of the self may help to understand more fully the subtle ways in which people change—in order, perhaps, to maintain their stability.

Lifespan development

The lifespan development perspective offers a theoretical framework which acknowledges that personality may develop from an interaction with both biology and the environment. This approach enables the ‘normal’ changes that occur due to the passage of time to be understood as part of ‘the ageing process’, by recognizing that ageing is influenced by earlier aspects of the life course (Baltes et al., 1980). Accordingly, human development continues throughout the entire lifespan, with old age being just another developmental phase. Baltes and Baltes (1990) summarized this psychological perspective on lifespan development into seven propositions about the nature of human ageing:

1. There are major differences between normal, pathological, and optimal ageing.
2. The course of ageing demonstrates much inter-individual variability (heterogeneity).
3. There is much latent reserve capacity in older age.
4. There is an age associated limitation to the range of reserve capacity.
5. Age-related decline in some aspects of cognitive functioning (speed, etc.) can be compensated by pragmatic knowledge (intelligence, reasoning).
6. The balance between gains and losses becomes less positive with increasing age.

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7. In old age the self remains resilient.

Underpinning these propositions are three sets of influences. The first set—normative age-graded influences—are those which have a relatively strong relationship with chronological age in terms of their onset and duration. These include biological maturation and age-related socialization, such as the family life cycle, education, and occupation. They are normative, in that the timing and duration are similar across individuals.

The second set of influences—normative history graded—are biological or environmental influences that occur in similar ways to most members of a specific population cohort. Examples of these influences would be wars or epidemics, or experiencing with one's age-peers a significant event or sequence of events in history.

The final set of influences—non-normative life events—occur independent of age or history, and their occurrence tends to be specific to the individual. These include factors such as unemployment, illness, winning a lottery, divorce, bereavement, institutionalization, or relocation. The 'joint impact of influences of the three types, mediated through the developing individual, accounts for the nature of lifespan development, for its regularity, and also for its differential properties in terms of inter-individual differences, multi-directionality and multi-dimensionality' (Baltes et al., 1980, p. 76).

The lifespan developmental perspective of ageing and its seven propositions offer a comprehensive picture of ageing, encompassing decline, change, stability, and growth, reflecting the three sets of influences on ageing described previously. They also emphasize the considerable variability and flexibility of older age, described as 'differential ageing' (e.g. Baltes et al., 1999).

Erikson's life-cycle model of personality development

Typically, developmental models with their roots in psychoanalysis focused on infancy, childhood and adolescence, with scarcely a nod towards adulthood. Erikson's Eight Stage Model of the Life Cycle stood out because it viewed personality development as continuing throughout the whole life cycle from childhood to old age (Erikson, 1963, see Table 49.1). This model describes how individuals may accomplish each life phase, emphasizing how the self/personality/identity develops in stages and results in fulfilment, and proposes that there is a biological predisposition to adapt at each of these distinct stages of the life cycle. It may be described as an interactional model of personality and environment, with the developing individual being affected by societal demands and requirements.

Table 49.1 Erikson's Eight Stages of the Life Cycle.

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Conflicting issues	Emerging value	Life period
1. Basic trust versus mistrust	Hope	Infancy
2. Autonomy versus shame and doubt	Will	Early childhood
3. Initiative versus guilt	Purpose	Play age
4. Industry versus inferiority	Competence	School age
5. Identity versus identity (role) confusion	Fidelity	Adolescence
6. Intimacy versus isolation	Love	Young adulthood
7. Generativity versus stagnation	Care	Maturity
8. Integrity versus despair (and disgust)	Wisdom	Old age

Source: data from Erikson. E. (1963). *Childhood and Society*. Harmondsworth: Penguin.

These eight periods of the life cycle originate in childhood. At each stage there is a conflict between two forces, and if development is to be successful, the conflict needs to be resolved in order to obtain an emerging human strength. The eighth (and originally final) stage is characterized by an evaluation of life, involving looking back and assessing whether it was a meaningful experience. Acceptance of life is crucial for achieving a sense of integrity or wholeness, with wisdom being the successful outcome. Alternatively, this review of life could lead to a conclusion that life was unproductive and meaningless, thereby resulting in despair.

Erikson's model was later extended by his widow, Joan (Erikson, 1998), to include a ninth stage of 'gerotranscendence' (Brown and Lowis, 2003). This draws in part on work by Tornstam (1992) and appears to have been prompted by the experience of both Joan and Erik Erikson in living well into their 80s. Gerotranscendence refers to an acceptance of the proximity of death without fear, a sense of release from material stresses, an enjoyment of quiet reflection, reduced self-centredness, and a positive disengagement. For Tornstam, this was a forward-looking process, associated with wisdom and with continued life satisfaction. Erikson

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(1998) associates the path to gerotranscendence with re-engagement with the negative poles of the previous eight stages; for example, the older person may have to confront their mistrust of their own abilities to remain independent, or their sense of inferiority in not being able to continue with previous roles. There is a strong sense of the spiritual, in its broadest meaning, in this proposed developmental stage.

Erikson's theory fits well with the proposition of the 'resilient self' of Baltes and Baltes (1990) and that older age can be accompanied by the acquisition of new behaviours important for ageing (Baltes et al., 1980). In terms of Erikson's stages, the continuing development of the self across the lifespan and the ultimate achievement of wisdom provide some explanation for the maintenance and growth of wellbeing in older age.

There is some empirical support for this claim. Ardel (2000) examined the benefits of wisdom in older age, with wisdom operationalized as cognitive, affective, and reflective personality qualities. Wisdom outweighed the contribution of objective conditions to the prediction of life satisfaction, and Ardel (1997) showed that wisdom had a higher impact on life satisfaction in old age than physical health, income, socioeconomic status, physical environment, or the extent of social relationships. Thus, the still-developing personality exerted a strong influence on wellbeing in later life.

Erikson's stage model introduces some important aspects of ageing. It reflects the continuous development of the self. It highlights the process of adaptation, which is achieved through tackling and resolving the conflicting issues at each life stage. Implicit in the model is the potential for earlier developmental tasks that are not completely resolved to re-surface at later points of the life cycle. For example, the person whose sense of inferiority is managed by additional investment in industriousness, in keeping busy and active, becomes vulnerable when retirement leads to a loss of purpose, or physical health problems enforce inactivity. Or the person who learned in infancy that others cannot be trusted finds dependency on others difficult to countenance, even though the support of others may clearly be required. Adaptation is crucial and is dependent upon how the factors that might either constrain or enhance the ability to reach full potential are negotiated. The emphasis on the development of the self in this life cycle theory also highlights the important role that inner psychological resources central to the self might play in successfully negotiating conflicting issues and achieving wellbeing.

Psychological resources in later life

Psychological resources central to the self are increasingly recognized as important in adaptation, development, and wellbeing in later life (Ryff, 2014). These psychological resources have a variety of labels, including self-efficacy, self-esteem, self-acceptance, environmental mastery, and sense of control. Resilience is increasingly being used (loosely) as a

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general term for these 'self' resources, which all reflect an inner strength that allows the person to assimilate changes and losses, and to find ways of coping and managing the situation and their own response to it, without threatening their sense of self-worth. More extensive changes or difficulties may require an accommodation of the self-concept, but those who age successfully maintain a strong core sense of self. In line with this, continuity theory (Atchley, 1989) argues that learning how to best adapt to change continues across the lifespan, and that wellbeing is achieved through adaptive choices that maintain the continuity of the self, while dealing with age-associated changes. Stability in older age then results from the active and ongoing interplay an individual has with their environment.

This section explores these resources in more depth and outlines five psychological resources important to ageing (self-esteem, perceived control, self-efficacy/competence, self-acceptance, and resilience). It discusses evidence for the relationship of each with age and presents their importance across a range of outcomes.

Self-esteem

Self-esteem refers to the person's evaluation of his/her self-worth, derived from values, goals, and aspirations (Rosenberg, 1979). Self-esteem features in research as an outcome measure, an intervening variable and as a resource to draw on when confronted with certain situations, although Orth and colleagues (2015) consider it should be seen as a personality trait.

Cross-sequential analyses of several large samples using the standard measure of self-esteem (the Rosenberg self-esteem scale) across the lifespan show consistently a curvilinear relationship between self-esteem and age (Orth et al., 2012; Orth et al., 2015). Self-esteem increases from adolescence to middle adulthood, reaching a peak at about age 50 years, and then decreases into later life. Although Orth and colleagues (2012; 2015) suggest that there is stability across cohorts, Twenge and colleagues (2017), re-analysing data from one of the samples, identified higher levels of self-esteem in later birth cohorts.

The association of self-esteem with a variety of other variables emerges from Orth and colleagues' (2012; 2015) analyses. Mood and affect, relationships, health, and work satisfaction all correlate with self-esteem.

Perceived control

Possessing a sense of control enables individuals to regulate and direct events, to participate actively in life, and to be independent and have self-responsibility (Wallhagen, 1998). As older adults seek to maintain control when facing losses associated with older age (Baltes, 1996; Fung, Carstensen and Lutz, 1999), control could be regarded as an important psychological resource in older age.

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The locus of control theory was proposed by Rotter (1966). Individuals with an 'internal locus of control' believe they have control over their successes and failures, while those who believe that their lives are controlled by other, external forces such as luck, fate, or the behaviour of another person are said to have an 'external locus of control'. Research findings support the beneficial effect of an internal sense of control in older people; for example, it is associated with less physical disability in women recovering from surgery for fractured neck of femur (Shaw et al., 2003) and predicts better life satisfaction in frail older people (Abu-Bader et al., 2002).

Age and gender differences in personal control have been reported, with older women having lower perceived control than men. This gender gap was greater among older people than in younger comparisons (Ross and Mirowsky, 2002). Mirowsky (1995) examined perceived control across an age range of 18 to 85. In the 18–50 age range it remained high, but declined with increasing age, with the oldest age groups having the lowest score. In a longitudinal study of adults aged initially 64–85, over a five-year period, perceived control decreased significantly, with changes associated with increased neuroticism and reduced conscientiousness (Kandler et al., 2015).

Schulz and Heckhausen (1996, 1998) distinguish two types of control: primary and secondary. Primary control refers to the immediate environment: changes are made by influencing the external world. Secondary control is based within the individual: the self is the source of change, the person adjusting to the situation, adapting goals and expectations. Both types of control are thought to assist in favourable development across the lifespan but have different paths. Primary control is most prominent in infancy and adolescence, with a peak around the age of 40–50 years, then a gradual decline into later life. Secondary control starts later in life, with a steady increase into older age (Magai, 2001; McAdams and Olson, 2010). The change from primary to secondary control across the lifespan may enable greater regulatory control of emotion and wellbeing, providing a valuable resource in older age. The two types of control need to be assessed differently, perhaps explaining why some earlier studies did not show a decline of perceived control in later life (e.g. Lachman and Weaver, 1998). Some measures may reflect secondary control more than others.

Perceived control emerges from longitudinal studies as both a precursor and an outcome of health and social support across adulthood and later life. Perceived control predicts later health and social support, but perceived control is also greater where initially health is better and more social support is available (Gerstorf et al., 2010). Infurna and colleagues (2011) report similar findings but add life satisfaction to the list of related variables involved in this positive feedback loop. Interestingly, these associations appear not to be greatly influenced by age, despite health arguably becoming much more of a salient issue.

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Self-efficacy/competence

The concept of competence can be thought of as covering three broad domains: the range and level of skills, personal belief about abilities (efficacy and mastery), and the adaptive fit between skills and environmental demands (Baltes et al., 1993). Personal efficacy/self-efficacy (Bandura, 1997) encompasses the belief that success can be achieved in what we want to do. It is also regarded as an evaluation based on a sense of competence (Dietz, 1996). A strong sense of efficacy increases the likelihood of a successful outcome, by affecting performance and intentions (Bandura, 1997). Estimates of predicted success or failure are derived from memories of the effects of previous activities; previous experiences of success or failure will determine whether the person believes they are *personally* capable—or not—of achieving a desirable outcome. Crucially, beliefs concerning personal efficacy influence thought patterns and subsequent performance.

Personal competence underlies the adaptive behaviour that is central to the person-environment transaction model (Lawton, 1989). This theory proposes that the person and the environment are joint determinants of behaviour and subsequent wellbeing. For example, older people with decreased physical functioning may need to draw on their resources and adapt their behavioural competence to the level of environmental demands experienced, in order to maintain positive subjective wellbeing (Lawton, 1989). Demands can come from a diverse range of environmental areas: interpersonal, suprapersonal, social, and physical. In this context, competence is an evaluative, cognitive process where the demands of the situation influence an individual's sense of efficacy (Wallhagen, 1998).

Welch and West (1995) describe how according to self-efficacy theory, older age is generally considered to be a time where the potential for positive effective behaviour is reduced. Negative stereotypes of ageing lead to cognitive changes being interpreted as failures and changes in physical functioning can make negotiating the physical environment difficult. Trouillet and colleagues (2009) identified little age-difference in self-efficacy in adults aged between 22 and 88. Problem-solving coping was predicted by self-efficacy and social support, but not by age—although their older sample tended to report having less social support.

In addition to measures of general self-efficacy, domain-specific measures are often used, examining self-efficacy in a specific context. In terms of the memory domain, levels of perceived memory efficacy were found to predict the extent of improvement in memory performance in both young and older adults after training in mnemonic aids (Rebok and Balcerak, 1989). Stephan and colleagues (2011) reported that higher memory self-efficacy was related to higher life satisfaction and subjective health and to lower subjective age in a sample of older people aged 60 and over. Thus, people who regarded themselves as younger than their chronological age had more confidence in their memory and enjoyed

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greater life satisfaction. An Italian study of adults aged 20–80 found that self-efficacy for positive affect, empathy, and social self-efficacy declined as age increased, although there were gender differences, with increased self-efficacy for negative affect across the age cohorts for females (Capara et al., 2003).

Self-acceptance

Ryff and Singer (1996) describe self-acceptance as a key dimension of positive psychological functioning, viewing it as an aspect of self-actualization, maturity, and optimal functioning emphasizing the acceptance of current and past life. It makes possible the maintenance of self-esteem when dealing with some of the less desirable aspects of personal life (Keyes and Waterman, 2004). Self-acceptance is crucial for achieving a sense of integrity, which is the final stage of Erikson's model of the life cycle.

Self-acceptance has been found to remain consistent across young, midlife, and older aged cohorts (Ryff and Singer, 1996), with males reporting significantly higher self-acceptance than females (Capara et al., 2003). The positive relationship between self-acceptance and subjective wellbeing in older adults is seen as enabling an acceptance of age-related changes (Ranzijn and Luszcz, 1999).

Resilience

The concept of resilience derived from the observation that people can still function positively although exposed to substantial stressors and risks, and recover quickly from set-backs (Rutter, 1995). Resilience can be viewed as the opposite to vulnerability, encompassing personal competences across cognitive, emotional, and social domains (Tizard and Clarke, 1992). Psychological resilience is thought to be important in late life as a component of successful psychosocial adjustment (Wagnild and Young, 1993) and Pruchno and colleagues (2015) suggest that successful ageing could be viewed as a pattern of resiliency across the lifespan.

A conceptual analysis of resilience (Windle, 2011) identified three necessary requirements for resilience: a significant adversity or risk; the presence of assets or resources to offset the effects of the adversity; and positive adaptation or the avoidance of a negative outcome.

Resilience was then defined as 'the process of effectively negotiating, adapting to, or managing significant sources of stress or trauma. Assets and resources within the individual, their life and environment facilitate this capacity for adaptation and 'bouncing back' in the face of adversity. Across the life course, the experience of resilience will vary' (Windle, 2011).

Although resilience can be defined, its measurement has proved challenging (Windle et al., 2011). Hardy and colleagues (2004) proposed that in older people, a positive response to a stressful life event is

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indicative of a resilient process. For example, Netuveli and colleagues (2008) defined resilience as 'bouncing back' from adversity; in a longitudinal survey, those exposed to adversity (e.g. bereavement or functional limitation) who after a year had returned to their pre-exposure level of psychological distress were identified as resilient. However, the conceptualization of resilience as the response to the stressful event has its limitations, in that it cannot be measured in the absence of a significant adversity.

The examination of resilience as an internal personality resource provides the opportunity to address this limitation, and a number of questionnaire measures have been developed. Rutter (1987) described resilient individuals as possessing self-efficacy, self-esteem, and a range of problem-solving skills. Others describe resilient individuals as possessing personal competence and acceptance of self and life (Wagnild and Young, 1993). These personality resources are thought to protect individuals in the face of adversity and lead to positive adaptive behaviour by acting as a protective 'buffer' (Rutter, 1987) or as compensatory factors that directly influence outcomes (Masten, 1999). In this context, resilience could be viewed as an 'umbrella' term for such psychological resources which are central to the self. Windle and colleagues (2008) provided some support for this, in that they identified a single common higher-order factor underlying self-esteem, personal competence (self-efficacy), and perceived control in a large sample of 1847 people aged between 50 and 90. Scores on this 'resilience' variable were lower in this cross-sectional survey in those aged 70 and above, with the highest scores in those age 60–69 (Windle et al., 2009). However, caution is needed in interpreting age differences in resilience scores, given the complexity of the construct and its measurement, and the potential differences in demands on resilience at different points in the life-course.

The importance of psychological resources to wellbeing

Research that has examined the influence that psychological resources have on wellbeing finds that they can have an intervening effect. They can increase the possibility of positive changes in health behaviours and wellbeing (Wells and Kendig, 1999), or can limit the potential negative influences on wellbeing of risk factors associated with ageing (Windle and Woods, 2004). In the latter study, a representative sample of 420 people aged 70 and above (mean age 78) were interviewed. Physical health limitations, loneliness, housing difficulties, and being widowed or divorced were related to lower levels of life satisfaction. However, the person's sense of environmental mastery mitigated the effects on life satisfaction of both physical health limitations and housing difficulties, and, to a lesser extent, of loneliness. In other words, having a strong sense of environmental mastery reduced the impact of the difficult circumstances the older person was experiencing.

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Self-efficacy has been found to buffer the impact of cancer on depressive symptoms in people aged 55–85 (Bisschop et al., 2004) and to diminish the negative impact of impaired functional capacity on depressive symptoms (Knipscheer et al., 2000). Self-efficacy probably influences the coping processes that people require when faced with problematic situations, and their subsequent choice of adaptive strategies (Slangen-de Kort et al., 2001). Reductions in perceived control over a five-year period have been related to reductions in wellbeing in older people initially aged 64–85 (Kandler et al., 2015).

Windle and colleagues (2009) found evidence for the protective effects of psychological resilience on wellbeing in the presence of ill health, but the relationship was slightly different in different age cohorts. In those aged 60–69 years, higher levels of psychological resilience were associated with high wellbeing whatever the level of ill health. For those aged 70–79 and 80–90 years, psychological resilience again provided an advantage overall, but for those with high levels of resilience there remained an association of ill health with lower wellbeing. In a sample of over 10,000 people aged 51–98, Manning and colleagues (2014) found that, over a two-year period, resilience protected against the negative impact of chronic disability in later life on day-to-day functioning. Not only did people with higher scores on their resilience measure have lower levels of disability, but also resilience buffered the effects of the onset of a new chronic condition in relation to subsequent disability.

The beneficial effects of such resources in older age may then be a key factor for wellbeing. Resources such as mastery, self-esteem, and optimism may be conceptualized as part of the core of the reserve capacity that provides a basis of resilience in older age (Gallo et al., 2005). These mechanisms of personal agency can help to give meaning to many external pressures, so that they can be dealt with successfully, with positive ageing being the outcome for those who are able to respond with resilience to the accumulating adversities across the lifespan (Pruchno et al., 2015).

The theory of selective optimization with compensation

The potential regulatory effect on wellbeing of the resilient self can be partially explained through the theory of Selective Optimization with Compensation (SOC, see Fig. **49.1**). The theory describes three processes which may be used in adaptation to changes occurring in later life.

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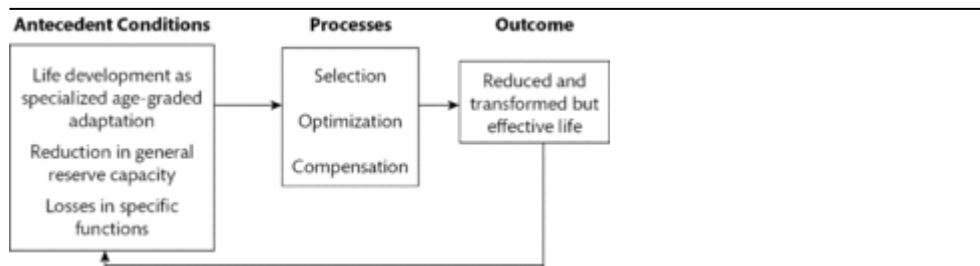


Fig. 49.1

The theory of Selective Optimization with Compensation, which describes three processes that may be used to adapt to changes occurring in later life.

Reproduced with permission from Baltes, P. B. & Baltes, M. M. (1990). Psychological perspectives on successful aging: The model of selective optimisation with compensation. In P. B. Baltes, and M. M. Baltes, (Eds.), *Successful aging: Perspectives from the behavioural sciences*. Cambridge: Cambridge University Press. Copyright (c) 1990 Cambridge University Press.

Selection implies an adjustment of expectations to permit personal control and satisfaction (Baltes and Baltes, 1990). It involves choosing goals, life domains, or life tasks. Selection may require a restriction to fewer domains of functioning due to new responsibilities and stresses—described as elective selection—or it may occur as a consequence or in anticipation of losses in certain areas of life, such as personal or environmental resources (loss-based selection). It may also refer to the avoidance of one domain, or a restriction of tasks or goals in one or more domains. Selection can also involve new goals, such as environmental changes (e.g. moving house due to difficulties with the current home) or a more passive type of adjustment (such as not climbing the stairs) (Baltes and Carstensen, 1999). Compensation and optimization provide the ability to maintain or even enhance chosen goals (Baltes and Carstensen, 1999). *Optimization* of behaviour occurs when losses are minimized and gains maximized and is the desired *outcome* of the SOC process. The methods a person has for achieving their goals are refined and perfected (Baltes and Carstensen, 1999). *Compensation* is required when skills and capacity are reduced below the level required for adequate functioning. In order to maintain or even optimize that prior functioning, a present skill may be adapted into a new behaviour, or new means sought to retain that functioning (Baltes and Carstensen, 1999). Freund (2008) reviews empirical studies that have provided evidence for the importance of the SOC model in understanding how individuals manage their resources and achieve their goals.

According to Herzog and Markus (1999) the theoretical perspective of the self system can assist in understanding such processes. They state that:

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the domains and dimensions that define the self provide the basis of selectivity, determining where time and energy will be invested, where efficacy and control (or the lack of it) will be experienced, what will be planned for, what will be compensated for, what will be discounted or ignored, and ultimately how individual lives accrue meaning and structure (p. 228).

In other words, the self can provide context and meaning, which, in turn, is developed from a view of the self from the past, present, and future perspectives. This process of self-reference can maintain a positive self-concept. In relation to ageing, how individuals react to changing roles and life events is dependent upon mediation by the self-concept (Markus and Herzog, 1991). The concept of resilience may then represent positive functioning across the diverse range of resources that characterize the self.

Personality and dementia

If personality can indeed be thought of as showing continuity over the lifespan, with individuals showing remarkable capacity to adapt and cope with difficult life circumstances, what are the effects of a dementia on personality, and does the person's personality influence the way in which dementia presents? McCrae (2002) suggests that 'the most dramatic and best-documented changes in personality are those associated with changes in the brain, attributable to Alzheimer's disease (AD) or to traumatic brain injury'.

Is personality a risk factor for dementia?

In recent years, a wide variety of potential risk factors have been examined in relation to their association with the development of a dementia later in life. In the psychological domain, most attention has been given to the potential for 'cognitive reserve' to delay the onset of dementia, with factors such as education and engagement in cognitively stimulating activities and pursuits thought to build an additional resource upon which to draw. Maercker and Forstmeier (2012) have extended this concept, under the title of 'motivational reserve', which encompasses aspects of how cognitive resources are used and developed, in terms, for example, of a sense of purpose (Boyle et al., 2010) and drive.

This broader view of psychological risk factors is now supported by a number of studies that highlight the role of various of the major personality traits in relation to predicting both cognitive decline in later life and the incidence of dementia. In reviewing the literature relating to cognitive function and cognitive decline in later life, Curtis and colleagues (2015) highlight the protective effect of higher levels of conscientiousness with respect to cognitive decline, although unrelated to level of cognitive function per se. Openness shows the opposite pattern, higher levels being positively associated with cognitive ability, but not with less decline. Neuroticism also appears to be related to aspects of

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cognitive function. Luchetti and colleagues (2015) provide results from a large-scale longitudinal study, along with a meta-analysis of five other prospective studies, in which nearly 14,000 older people, with a mean age of 68.8 years, were followed up for four years. The association between higher neuroticism and lower conscientiousness and cognitive decline were evident in both the meta-analysis and the large follow-up study. In the latter, there was also evidence that higher openness was associated with less decline in memory performance.

Low and colleagues (2013) reviewed studies examining the association between personality and incidence of dementia; they included 15 studies in a meta-analysis and concluded that conscientiousness reduced risk of developing dementia, while neuroticism increased risk. Extraversion and agreeableness showed no association with dementia, but the evidence for the protective effect of openness was inconclusive. Terracciano and colleagues (2014) reviewed evidence from five prospective studies, with similar results, although there was again a more tentative suggestion that openness, along with agreeableness, might have a protective role. They also reported results from a follow-up of up to 22 years of 1,671 participants in the Baltimore Longitudinal Study of Aging, and identified that the risk of developing a dementia was increased considerably for those with high neuroticism and for those with low conscientiousness scores.

More recently, Terracciano and colleagues (2017), following over 10,000 people for up to eight years, provide further support for the association of neuroticism and low conscientiousness with the development of both dementia and of milder levels of cognitive impairment. Lower agreeableness was also associated with greater risk of developing dementia. The personality risk factors for dementia incidence remained significant even after controlling for other common dementia risk factors such as education, age, diabetes, and hypertension.

The question arises as to why aspects of personality might be related to cognitive decline and to dementia incidence. Terracciano and colleagues (2014) suggested that part of the explanation could be the association between personality and lifestyle, with low conscientiousness and high neuroticism being linked with obesity, inactivity, and smoking, all risk factors for dementia. They point out that high neuroticism is associated with depression, another established risk factor (e.g. Wilson et al., 2004). However, as noted, this research group subsequently reported that the link between personality and dementia incidence remained after controlling for a number of these risk factors (Terracciano et al., 2017).

In a report of 309 participants who had undertaken frequent cognitive assessments in longitudinal studies, who had died (mean age 87.6 years), and whose brains had been examined at post-mortem, Wilson and colleagues (2015) were able to examine trajectories of cognitive decline, for an average of 10.7 years prior to the person's death. They identified that, on average three years before death, there was a period of steeper

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cognitive decline much more pronounced than the gradual decline in preceding years. Higher conscientiousness (assessed at baseline) was associated with slower terminal decline, but not with the gradual decline preceding this. This effect remained after taking into account the extent of neuropathological changes evident at post-mortem. This suggests that high conscientiousness may contribute to cognitive reserve, influencing the degree of impairment arising from a given extent of neuropathological change. A similar conclusion may be drawn from Terracciano and colleagues (2013) analysis of a cohort of 111 people evaluated for Alzheimer pathology at post-mortem. They describe a 'resilient personality profile', including higher conscientiousness and lower neuroticism, as self-reported on average 15 years previously, associated with a greater probability of remaining clinically asymptomatic in the presence of Alzheimer-type neuropathology.

Segerstrom (2018) discusses several possible pathways for the personality/incident dementia linkage, focusing on AD specifically. These include a common 'cause', such as a gene; personality predisposing the person to AD risk, through health behaviours; personality affecting the appearance or severity of AD, as perhaps with cognitive reserve, a 'pathoplastic' effect, or resilience to neuropathology; and personality change (towards lower conscientiousness and/or higher neuroticism) forming part of the AD spectrum, occurring decades prior to a diagnosis being made. Distinguishing these potential mechanisms will not be easy, but Segerstrom concludes that predisposition and/or a pathoplastic effect appear most promising.

Does dementia change personality?

In evaluating personality change in people with dementia, researchers must usually rely on a relative completing two personality inventories, one for how the person is now, and one for a period well before the onset of the condition. This involves two assumptions; firstly, that proxy reports of personality can be reliable and valid; and secondly, that retrospective accounts can be accurate, and not influenced by the dementia-related changes, or by the relative's experience of care-giving. The reliability and validity of the proxy version of the NEO-PI scale has been well documented (McCrae and Costa, 2003). Evidence for the second assumption is provided by Strauss and colleagues (1993), who report ratings of 22 people with AD by two informants (the main caregiver and another relative or friend), showing substantial agreement between the raters, both in comparative rankings and in absolute level on the NEO-PI scale.

A number of studies have used the NEO scale, placing the results in the context of contemporary personality research. Robins-Wahlin and Byrne (2011) report a systematic review of such studies. They identified nine studies, with a total of 291 participants, with the individual studies being relatively small in size (range 19–50). The findings were consistent across studies; a major increase in neuroticism and decrease in

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conscientiousness were identified (of the order of 1–2 and 2–3 standard deviations, respectively). The other factors—extraversion, openness and agreeableness—all showed consistent reductions across studies also. The findings fit well with those regarding personality factors predicting dementia reviewed earlier.

These findings on change between pre-morbid and current personality as rated retrospectively by an informant are broadly supported by studies where the current personality ratings of people with dementia have been compared with a control group of similar age but without dementia. A meta-analysis of such studies has been reported by D'Iorio and colleagues (2018), including ten studies. People with AD had significantly higher levels of informant-rated neuroticism, and lower levels of conscientiousness, openness, agreeableness, and extraversion than comparison groups. The results were similar where people with AD had rated their own personality, except that they reported similar levels of conscientiousness and agreeableness to the comparison groups.

Several studies have begun to explore whether the reported personality changes are specific to AD, or are a more general feature of neurodegenerative disorders. For example, Torrente and colleagues (2014) report changes in informant ratings of personality (current vs ten years ago), in a mixed sample of 50 patients. The changes were broadly similar for people with diagnoses of AD, primary progressive aphasia (PPA) and behavioural-variant frontotemporal dementia (bv-FTD). The exception to the pattern of higher neuroticism, lower conscientiousness, and lower extraversion was for bv-FTD, where no change in neuroticism was noted. Lykou and colleagues (2013) report similar results for a small sample (total 42) of people with AD, mild cognitive impairment, and bv-FTD, with the latter group showing reduced neuroticism compared with the pre-morbid rating.

Although more research is needed, the robustness of the personality changes reported and consistent findings across studies and samples suggests that they may reflect adaptation to neurodegeneration, as well as the potential for resilience to the effects of neuropathology discussed previously. Thus, the reduction in extraversion may reflect the withdrawal from social contact and social roles typically seen in dementia; the reduced (informant-rated) conscientiousness may arise from difficulty in maintaining previous standards in view of the cognitive impairment; and the increased neuroticism may reflect the presence of increased uncertainty and vulnerability for the person with dementia. In bv-FTD, plausibly the specific neuropathology provides some protection from these worries and concerns.

In contrast to these consistent changes in personality, evidence is emerging of stability in self-concept (Clare et al., 2012). The Tennessee Self Concept Scale (short-form) was completed by 95 people with early-stage dementia in the MIDAS study, and scores were consistent with normative values and distribution. Over a 20-month period, scores did not

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change significantly, although there was a downward trend. Lower self-concept scores were related to higher scores on depression and anxiety scales and on a memory test; potentially, those with better memory are more able to recall and recognize the changes occurring. Discrepancies with a carer's rating of the person's self-concept on the same scale were small, and were predicted by level of caregiver distress. Maintaining self-concept appeared to be important for the maintenance of quality of life in this sample.

Does personality influence dementia presentation?

Kitwood (1997) included pre-morbid personality as one of the variables influencing dementia presentation, and there is some evidence that personality variables influence quality of life of people living with dementia. For example, higher self-reported conscientiousness as well as a more positive self-concept were associated with better quality of life as rated by the person with dementia in the MIDAS study (Woods et al., 2014). The relationship of conscientiousness to quality of life was explained in part by the associations between conscientiousness and self-concept and with lower depressed mood.

There has also been interest in whether behaviour that challenges in dementia may relate to pre-morbid personality traits. In other words, do certain personality traits lead to the person with dementia being more vulnerable to experiencing distress and interpersonal difficulties. Osborne and colleagues (2010a) conducted a systematic review of this relationship and identified 18 eligible studies involving 1,417 people with dementia where the studies had made use of a comprehensive pre-morbid personality assessment. They report that 72% of the studies reviewed did find a significant relationship between pre-morbid personality and behaviour. Pre-morbid neuroticism was related, perhaps unsurprisingly, to mood, but also to aggression and overall behavioural problems. There were also suggestions that those who were rated as less agreeable in earlier life were more likely to be aggressive and those who were rated as having been extraverted were less likely to wander.

Other studies, not included in Osborne and colleagues' review, provide mixed support for the overall findings. Whall and colleagues (2008) report a small but significant association between lower pre-morbid agreeableness and aggression during a shower bath, but Beck and colleagues (2011) report that *higher* pre-morbid agreeableness was related to (non-aggressive) persistent vocalization. This is a timely reminder that the factors underlying different types of challenging behaviour may well be different. Pocnet and colleagues (2013) failed to identify a relationship between pre-morbid personality and behavioural problems in people in the early stages of AD. They point out that personality does typically change as dementia develops (as mentioned previously), and at the same time behavioural problems may well develop, but that any causal relationship between the two is likely to be complex.

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Sutin and colleagues (2018) report analyses of data from a large population study (the Health and Retirement Study), identifying 1,988 participants who had shown cognitive impairment before death, and who had completed a self-report personality measure up to eight years previously. An informant was asked whether a number of behavioural problems had occurred during the last year of the person's life. Higher levels of self-reported neuroticism were associated with a number of problems at the end of life, including depression, hallucinations, wandering off, not being able to be left alone, and uncontrolled temper. These associations were evident irrespective of age, gender, race, or education. Lower conscientiousness was associated with a higher risk of needing someone constantly with the person and with getting lost in familiar places, but was associated with fewer symptoms overall. Agreeableness was associated with less risk of getting lost and extraversion with depression, whereas openness was not associated with any of the behavioural problems included. Although there are advantages to self-report personality ratings, the relatively brief period between the personality rating and the occurrence, if any, of the behavioural problems makes it difficult to be certain to what extent the associations reported relate to life-long traits as opposed to changes in personality related to dementia and its prodromal period.

There has been some considerable interest in the effect of the attachment style of the person with dementia on their behaviour and adjustment (e.g. Miesen, 1993). Attachment style in adulthood is thought to reflect early experiences of parenting, with typically three main styles identified: secure; insecure-ambivalent; and insecure-avoidant. These styles provide a basis for personality traits such as neuroticism, extraversion, and agreeableness.

Magai and colleagues (1997) report results from a group of 27 people with mid to late dementia. Relatives rated lifelong attachment style, and ratings of the person's current emotional state were made by family, care staff, and independent observers. People with dementia rated as having a secure attachment style appeared to show greater positive affect, whereas ratings of pre-morbid hostility were related to ratings of current anger, disgust, and contempt. In a much larger sample of 168 people with mid to late dementia, Magai and Cohen (1998) found that people who were rated by relatives as insecure-ambivalent had increased levels of depression and anxiety. Those rated as insecure-avoidant had higher levels of activity disturbance and paranoid symptoms. Caregivers of people rated as having secure attachment styles reported less overall burden than caregivers of people with dementia who had life-long insecure attachment styles. Browne and Shlosberg (2005), in a sample of 53 people with dementia living in care homes, found that those rated as having life-long insecure-avoidant attachment styles showed more overt attachment behaviours (e.g. following staff, clinging onto visitors) than those rated as securely attached. However, Osborne and colleagues (2010b) report that 'parent fixation' was greater in people with dementia

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rated as having *lower* levels of insecure anxious (ambivalent) attachment. Parent fixation, defined as the belief that one or other parent was still alive, was also more common in those who were rated as having higher pre-morbid levels of conscientiousness. Neither attachment style nor pre-morbid personality predicted the presence of behavioural consequences of such a belief, such as calling out for a parent or seeking to return to the parental home.

In summary, it appears that there is some evidence that aspects of current and pre-morbid personality are related to the current quality of life, emotional state, and behaviour of the person with dementia, but the precise nature of the relationship needs further exploration. Given that ratings of pre-morbid personality often rely on family members as informants, using other informants for current function is essential to avoid spurious associations that reflect the impact of caregiving rather than an accurate appraisal.

Conclusions

This chapter firstly presented the debate regarding stability and change in personality across the lifespan, especially in relation to the 'Big Five' five-factor model. There is much evidence, in general, for continuity and consistency, but some changes are widely accepted, such as reduced neuroticism and greater conscientiousness. Lifespan developmental models emphasize that change may well be required to maintain stability in the face of changing external and internal circumstances and events, and Erikson's model provides a broad-brush approach, identifying a developmental task specific to later life, reflecting the potential for continued growth.

The model of selective optimization with compensation indicates how individuals can deal with ageing and the age-related tendencies for increased losses and fewer gains, making use of regulatory processes (Baltes, 1993). It has been proposed that the regulation of subjective wellbeing can occur through psychological resources that promote adaptation to adverse situations (Smith et al., 1999; Staudinger et al., 1999). Continuity theory would imply that a lifetime accumulation of experience would aid the development of a resilient self over the years, and this could explain how the self might be the link between various domains of life and wellbeing. Resilience is presented as a concept that captures the reality of development into later life, where the self faces many difficulties, losses, and threats, and yet seeks to maintain wellbeing. Research that has examined the role of resources such as mastery, self-esteem, optimism, and perceptions of social support and social conflict has conceptualized these resources as the core of reserve capacity that provides a resilient basis in older age (Gallo et al., 2005). Although the literature points to the importance of these psychological resources in older age, it is less clear about the maintenance of these resources in the oldest cohorts. The psychological resources that underpin resilience may

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provide the basis for the maintenance of wellbeing in older age, but it may be that there is an optimal time for their benefit.

In the context of dementia, evidence is emerging of consistent personality changes, especially relating to increased neuroticism and reduced conscientiousness. However, the picture is less clear with respect to the association of pre-morbid personality and current behaviour, except perhaps in relation to neuroticism and depression/anxiety. There is great scope for further work exploring the self in dementia, and the influence of factors such as resilience in this most demanding of challenges.

Finally, Hooker (2002) describes a three-level model of personality, of which the first two have been the main focus of this chapter. Level I relates to traits, as in the five-factor model; Level II includes self-regulatory processes, such as self-efficacy and control processes. Level III reflects the person's life story and is seen in activities with a social component such as remembering, reminiscence, and story-telling. It is also at the heart of Erikson's eighth stage, where the person's life review can enable meaning and coherence to be found in the varied experiences of a life lived. Hooker suggests that 'personality is most clearly revealed in later life', and it is ultimately in the person's life story narrative that the richness and meaning of the individual's personality can be discerned. Personality measures are rarely used in clinical practice (in the UK at least), but careful listening to the person's life story may well, ultimately, be far more informative than a profile of scores from an assessment battery, however useful they may be in a research context.

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Sexuality in older age

Chapter: Sexuality in older age

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Introduction

Sexuality is a central part of human life, and remains important across the life-course (Carpenter and DeLamater, 2012). However, sexual activity and late adulthood have typically been positioned as incompatible in public discourses. The deeply entrenched view of the sexless older person has been repeated and reinforced, often unintentionally, in various ways over the past 100 years. For example, Western medical regimes of knowledge, through their focus on treating disease, position old bodies as dysfunctional bodies in decline, including sexual decline. Furthermore, public policy relevant to sexual health has tended to promote ageism through the neglect of older adults in key policy documents such as the UK *National Sexual Health Strategy* (Department of Health, 2001). In wider society, and popular media in particular, a reluctance to pair sexual agency with older adults serves to reinforce the view that sex is the preserve of the young (Gill, 2008). The combined force of these powerful

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discourses and highly visible messages in Western societies has meant that later life sexuality has seldom been acknowledged.

However, over the past 30 years this has started to change. The sexual agency of older adults and their sexual health and wellbeing needs are now being recognized. Research in the area of older age sexuality has grown during this time, and there is now consistent evidence that sexual activity is important to the quality of life of many older adults. Sexual activity and satisfaction have been acknowledged for their benefits to wellbeing and physical health in older age (DeLamater, 2012; Træen et al., 2017a). And many people aged 60 and older (78% of women and 91% of men) consider sexual activity as important to their sense of wellbeing (Ferris, Smith et al., 2008) (more later). Nonetheless, health professionals can find it difficult to communicate about sexual matters with their patients. This chapter discusses the numerous reasons for this, and ageism is a major factor.

Ageism is pervasive and taken for granted, and has been described as being more socially condoned in Western societies than racism and sexism (North and Fiske 2012). Ageism can be exacerbated when older age intersects with other social categories such as sexual orientation, gender identity, socioeconomic position, and race/ethnic group. Older adults can face multiple stigma and being part of a marginalized group can have significant consequences as members not only lose power, but also face other inequalities (Calasanti and Slevin, 2006). According to the World Health Organization, sexuality encompasses 'sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy and reproduction' and is 'experienced and expressed in thoughts, fantasies, desires, beliefs, attitudes, values, behaviours, practices, roles and relationships'. So, when older age is coupled with sexuality, which is highly politicized and 'subject to power relations in both the private and public domains' (Heidari, 2015, p. 1), older adults can experience discrimination on a number of intersecting levels.

The majority of research on ageing and sexuality is conducted in high- and middle-income countries, which creates a bias in the evidence base. Where possible, we have included evidence from non-Western countries, but recognize that our chapter is predominantly Western focused. Similarly, the literature is biased towards those who are heterosexual and cisgender. So, we recommend caution when applying the literature in this chapter to those with non-binary gender identities and diverse sexual orientations.

We have included guidance to help professionals to be aware of sexuality issues that may affect their patients, as well as suggestions to help them open a dialogue. This guidance is suitable for patients of any sexual orientation. We have described our 'Three Ps' framework: Privacy, Permission, and Practice, which provides practical advice on talking to patients about sex, including how to start the conversation, and ways to facilitate comfort for both the patient and health professional. Many

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professionals carry their biases into their work, and are often unaware that these biases influence the way they respond to other people. For this reason, we have included an activity aimed at helping professionals explore their own practice and awareness of sexuality issues. But first, we discuss the key areas in the field of older adults and sexuality, starting with sex in later life, the sexual rights of older adults, sexual health, sexual violence, sexual communication and consent, sexual difficulties, and the barriers that older adults and health professionals face when communicating about sex in a healthcare context.

Sex in later life—a snapshot

Contrary to the stereotype that older adults are ‘asexual’ or no longer interested in sex, a growing body of research evidence suggests that many older individuals remain sexually active (Fileborn et al., 2015a; Fileborn et al., 2015b; Gott, 2001; Gott and Hinchliff, 2003; Gott et al., 2004; Minichiello et al., 2004). Although rates of sexual activity decline as we age, and particularly as we enter ‘deeper’ older age (Field et al., 2013; Karraker and DeLamater, 2013; Lindau et al., 2007; Schick et al., 2010), it is clear that many continue to engage in a diverse array of sexual practices across the life-course. U.S.-based research by Herbenick and colleagues (2010), with a nationally-representative sample of adults up to age 94, found that 53.5% of 60–69-year-old men, and 42.9% of men aged 70 and older, had vaginal intercourse in the past 12 months. 34.3% of 60–69-year-old men, and 24.3% of men aged 70+, reported performing oral sex on a woman. For older women, 23.4% of 60–69-year olds, and 6.8% of those in the 70+ category respectively reported having vaginal intercourse in the past 12 months. Women in these age groups were slightly more likely to report receiving oral sex from a male partner in the past 12 months, with 24.8% of women age 60–69, and 7.8% of women 70+ having done so.

The extent to which older adults are viewed as sexually active also depends on how we define ‘sex’, with older adults themselves tending to define sex in a broad way (Fileborn et al., 2016a; Gott, 2005; Helmes and Chapman, 2012; Karraker and DeLamater, 2013; Sandberg, 2013b; Trudel et al., 2014). U.S.-based research, for example, found that those in their 50s and older were more likely to have engaged in masturbation, rather than partnered sexual activity, in the past 12 months (Herbenick et al., 2010). Trudel and colleagues (2014, p. e45) further argued that older adults’ sexual desire may be better understood as ‘a characteristic of wanting more varied sexual activities with less genital activity, less based on performance, and could be characterized by persisted interest in sexuality in a broad sense’. As such, studies which focus on penetrative sex may underestimate the extent and richness of older adults’ sexual lives (Minichiello et al., 2004).

Research has consistently illustrated that sex in later life is highly gendered, with men reporting greater levels of sexual interest and activity, and placing a higher level of importance on sex, in comparison to

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women (Bergstrom-Walan and Nielsen, 1990; DeLamater and Koepsel, 2015; Karraker and DeLamater, 2013; Lindau et al., 2007; Minichiello, Plummer and Loxton, 2000, 2004). The reasons for this gendered disparity appear to relate largely to gendered norms regarding the acceptability of sexual desire and expression, the decrease in availability of sexual partners for heterosexual women as they age, and heterosexual women tending to partner with men who are older than them (Berdychevsky and Nimrod, 2016; DeLamater, 2012; DeLamater and Sill, 2005; Gott, 2001; Karraker and DeLamater, 2013; Lindau et al., 2007; Schick et al., 2010).

What shapes rates of sexual activity in later life?

Continued participation in consensual sexual activity, broadly defined, has been associated with a range of benefits (DeLamater, 2012), including an increased sense of wellbeing (Berdychevsky and Nimrod, 2016), better physical and psychological health outcomes (DeLamater, 2012; DeLamater and Koepsel, 2015; Gott and Hinchliff, 2003), physical pleasure and enjoyment (Berdychevsky and Nimrod, 2016; Fileborn et al., 2016a; Weeks, 2002), strengthened relationships, and enhanced intimacy (Berdychevsky and Nimrod, 2016; Fileborn et al., 2016a; Heiman et al., 2011; Trudel et al., 2014; Weeks, 2002). However, poor health is associated with reduced sexual activity (Field et al., 2013; Karraker and DeLamater, 2013; Lindau et al., 2007), and it is unclear whether sexual activity directly contributes towards 'good' health and wellbeing, or whether those who are already healthy are more likely to have sex.

Reduced interest or participation in sexual activity is associated with a range of complex factors that extend beyond simplistic biological and functional decline models of sexuality (DeLamater and Still, 2005; Hinchliff, Gott and Ingleton, 2010; Gott, 2005; Minichiello, Plummer and Loxton, 2004). For example, older adults may reprioritize the importance of sex in their lives upon the loss of a partner or the onset of significant health issues (Gott, 2005). DeLamater and Sill (2005) proposed that we should take what they term a 'biopsychosocial' model of sexuality in later life. They argue that sexual desire and function are shaped by a range of complex, intertwining factors including (DeLamater and Sill, 2005, p. 138; see also DeLamater, 2012):

- Biological: such as good or poor physical health, hormone levels, use of medications, and physiological function of our sexual organs as we age;
- Psychological: such as depression and other mental health challenges, our learned attitudes towards and beliefs about sex and sex in later life (for example, adhering to the belief that sex in later life is 'inappropriate'; see also Weeks, 2002), and the information or education we have received about sex and sexuality, and;
- Social: such as having a sexual partner, relationship duration, relationship quality and satisfaction (with those who are more satisfied

with their relationships reporting higher levels of sexual activity), and socio-economic status

Sex can be an important part of older adults' lives and sense of identity (Berdychevsky and Nimrod, 2016; Fileborn et al., 2016a). However, this is not to say that older individuals express themselves sexually in the same ways as their younger counterparts, or that there is no change in sexual function, desire, or identity (Trudel et al., 2014). Rather, it is to acknowledge that these changes do not result in older adults' sexual lives and sexual expression being 'less than' those of younger people (Fileborn et al., 2016a; Sandberg 2013a; Trudel et al., 2014). It is likewise important to recognize and acknowledge the diversity in older adults' desires and experiences: some individuals may indeed lose interest in sex as they come into later life (De Lamater and Sill, 2005; Karraker and DeLamater, 2013; Lindau et al., 2007). Older heterosexual women, for example, can express a sense of relief at no longer having penetrative sex (Berdychevsky and Nimrod, 2016; Fileborn et al., 2015a). Thus, in recognizing the rights of older individuals to remain sexually active, we must simultaneously acknowledge and respect their rights to *not* engage in sexual activity. Additionally, partnered sexual encounters should be mutually desired and consented to, and we address the emergent issue of sexual violence against older adults and sexual consent later in this chapter.

Shifting relationship contexts

In understanding the sexual lives of contemporary older adults, it is vital to consider the changing social and cultural contexts in which their sexual and romantic relationships are taking place. 'Baby Boomers'—those born in the decades following the Second World War—are commonly heralded as approaching sex and ageing differently to earlier generations, challenging pre-established norms of an asexual later life (Adams et al., 2003; Bourne and Minichiello, 2009; Fileborn et al., 2015a,b; Gott, 2006; Kirkman, Dickson-Swift and Fox, 2015). Within the Anglophone West, many of those coming into later life lived through the sexual revolution of the 1960s and gay and lesbian rights movement of the following decades, witnessed substantive changes to sexual norms and the acceptability of casual sex and sex outside of marriage, further aided by the development of reproductive technologies such as the oral contraceptive pill (Fileborn et al., 2015a; Gott, 2005; Kontula and Haavio-Mannila, 2009; Lyons et al., 2015; Nash et al., 2015; Smith et al., 2010). The introduction of no-fault divorce, and shifting acceptability of repartnering after the end of a marriage or death of a spouse likewise opened up opportunities for sexual and romantic relationships later in life (Bateson, Weisberg, McCaffery and Luscombe 2012; DeLamater, 2012; Gott, 2006; Nash et al., 2015; Smith et al., 2010). Developments such as online dating have revolutionized the process of meeting new romantic and sexual partners, and older individuals are embracing their use

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(Adams et al., 2003; Bateson et al., 2012; Malta, 2007; Malta and Farquharson, 2014).

Relationship styles and structures are likewise shifting. There is evidence to suggest, for example, that older adults are engaging in casual dating to a greater extent than their predecessors (Sears-Roberts Alterovitz and Mendelsohn, 2011). Some older women are also remaining single by choice, unwilling to (re)enter into new heterosexual relationships particularly where they may be expected to take up traditional gender roles based on 'wife' or 'carer' (Fileborn et al., 2015a,b). Others are 'living apart together', where couples form long-term relationships while maintaining independent living arrangements. Qualitative Australian research has documented older individuals engaging in what might be considered 'non-traditional' relationship styles (Kirkman et al., 2015). This includes 'friends-with benefits relationships', in which 'people have a friendship which includes a sexual relationship that is repeated or ongoing, yet do not live together or call themselves a couple' (Kirkman et al., 2015, p. 267), and open or non-monogamous relationships. Conversely, couples may divorce or separate yet remain living together, and this can again shift the sexual and power dynamics of the relationship. While evidence for these innovative relationship styles is largely based on small-scale qualitative research, it is nonetheless clear that sexual and romantic relationship arrangements are changing. We can no longer assume that heterosexual, monogamous marriage for life is the 'norm'.

Together, these significant social, cultural, legal, and technological advances have arguably increased both the acceptability of, and opportunities for, engaging in new romantic and sexual relationships in later life. These changes have also put the sexual health and wellbeing of older cohorts on the agenda, perhaps for the first time. As we outline in this chapter, it is becoming increasingly apparent that the sexual health and wellbeing of older adults must be included in health practice and policy.

The sexual rights of older adults

The increasing recognition of the sexual agency and sexual expression of older adults, alongside broader societal awareness of gender identity and sexual orientation, has prompted calls for the sexual rights of older adults to be acknowledged and met. Research on the sexual health and sexual wellbeing of older adults has been slowly growing. And research that explores sexual orientation in older age, and its connection with healthcare, is beginning to thrive (see, for example, Barrett et al., 2015). Such work is helping to shape the sexual rights arena, even though very few attempts, in research and practice, have focused specifically on the topic of the sexual rights of older adults.

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One reason for this may be because sexual rights have been considered predominantly in relation to young people. Traditionally, sexual rights have been promoted as a young person's issue because of the reproductive focus of public health. The umbrella of 'sexual and reproductive health' has excluded anyone who sits outside of this (narrow) definition, including those in same-sex relationships, and those deemed to be passed reproductive age. While young people are certainly more at risk of unintended pregnancies, and of acquiring a sexually transmitted infection (STI), older adults have been stereotyped as people who are not sexually active, and certainly not people who take sexual risks (we challenge this view later in the chapter). Assumptions such as these have worked to prevent progress in the area of the sexual rights of older adults.

Viewing sexual rights solely within the context of young people reflects the neglect of older adults from the area of sexual health overall. It is as though issues related to sexuality simply do not matter to older adults, or do not have relevance to their health and healthcare. However, this has started to shift and sexual rights have begun to be applied broadly. The influence of activist groups with an interest in the rights of marginalized groups, e.g. lesbian, gay, transgender, intersex, have played a role in helping to shape the sexual rights agenda away from a narrow reproductive focus. The sexual rights of older adults are beginning to be taken seriously, and a clear sexual rights agenda is being set by those who work with older adults and who can transform the service provision landscape.

In 2018, Barrett and Hinchliff proposed a sexual rights framework for older adults based on the Declaration of Sexual Rights from the World Association for Sexual Health. The framework connects fully with human rights, emphasizes empowerment, acknowledges diversity, and recognizes sexual pleasure (Barrett and Hinchliff, 2018). It has 15 key domains (Box 50.1).

Box 50.1 Sexual rights framework for older adults

The right to:

1. Equality and non-discrimination
2. Life, liberty, and security
3. Autonomy and bodily integrity
4. To be free from torture and cruel, inhuman, or degrading treatment or punishment
5. To be free from all forms of violence and coercion
6. Privacy
7. The highest attainable standard of health, including sexual health
8. Enjoy the benefits of scientific progress and its application

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9. Information
10. Education and the right to comprehensive sexuality education
11. Enter, form, and dissolve marriage and other similar types of relationships
12. Freedom of thought, opinion, and expression
13. Freedom of association and peaceful assembly
14. Participation in public and political life
15. Access to justice, remedies, and redress

A sexual rights framework is required because not all who work in aged care, including health professionals and service providers, are aware that sexual rights can and should be applied to older adults. In these instances, unintentional violations of sexual rights can occur. The framework, when applied in professional practice, will ensure that older adults are treated with dignity and respect, and are able to contribute towards informed decisions about their health and wellbeing. It will help to address inequalities in practice and service provision. Applying a rights-based framework to practice and service delivery can therefore help to promote awareness among staff, and to improve health services. Education that is built on a sexual rights framework can improve patient outcomes, and may be of particular relevance to the psychiatric context with regard to helping to prevent sexual risk behaviours (discussed further on).

Research in the area of older adults' sexualities has identified key recurring themes: invisibility, silencing, prejudice, discrimination, and lack of awareness and understanding from professionals (see Barrett and Hinchliff, 2018). A key obstacle to promoting the sexual rights of older adults, and ensuring that accessible and appropriate support is available, is the resistance to sexual rights per se across the world (Scientific and Technical Advisory Group and Gender Rights Advisory Panel, 2017). This is confounded by the current lack of a specific human rights convention for older adults. But a sexual rights framework for older adults is necessary and desperately required. Ageist attitudes and behaviours can affect *all* aspects of health and social care, with potentially damaging consequences.

Key Points

- Older adults have sexual rights.
- A sexual rights framework protects people from prejudice and discrimination.
- Service delivery and practice that employ a sexual rights framework will see better patient outcomes.

Sexual health and sexually transmitted infections in later life

Being older should not prevent clinicians from considering STIs in their patient group. While many are aware that people with severe mental illness can engage in sexual risk-taking, and thus high diagnoses of STIs are made (De Hert et al., 2011; Hallett and Rees, 2017), there may be less awareness that STIs are increasingly diagnosed in older age groups. STIs are on the rise among older individuals across Western countries including the US, Canada, the UK, and Australia (Bodley-Tickell et al., 2008; Minichiello et al., 2012; Spring, 2015). STI surveillance reports show that, although older adults face a considerably lower risk of new STI infection compared to younger age groups, STI rates in older populations have, nonetheless, steadily increased. STI surveillance data from the UK, for example, show that rates of chlamydia in the 65+ age group increased from 1.6 per 100,000 to 3.0 per 100,000 from 2011–2015 (Public Health England, 2015). Over the same time period and age group, gonorrhoea infections increased from 0.9 to 1.8 per 100,000 (Public Health England, 2015).

Older adults may face some unique risks when it comes to STI transmission. Reduced production of ‘natural’ lubrication and thinning of the vaginal wall can place older women at a greater risk of STIs due to the increased likelihood of cuts and tears facilitating transmission (Minkin, 2010; Slinkard and Kazer, 2011; Spring, 2015). The routine omission of older adults from sexual health educational campaigns and policy works to construct safer sex and sexual health as a ‘young person’s’ issue of little relevance to older individuals (Bodley-Tickell et al., 2008).

What do we know about safer sex practices of older adults?

Research to date indicates that, while older individuals use a range of safer sexual practices, they typically do so in inconsistent and context-dependent ways (Bourne and Minichiello, 2009; Fileborn et al., 2017a; Foster et al., 2012; Reece et al., 2010). Condom use, for example, tends to occur at higher rates in new or casual relationships (Schick et al., 2010), and may be phased out or not used if a partner is perceived as ‘trustworthy’ (Fileborn et al., 2017a), while those who are single report higher rates of condom use than those in relationships (Bourne and Minichiello, 2009; Reece et al., 2010). This suggests that decisions about safer sex may be based on value judgments, rather than knowledge of STI status. The use of value judgments was further evidenced in another Australian study, which found that although women over age 40 were more likely to talk to a sexual partner about STIs than their younger counterparts, they were ‘less likely to refuse sex without a condom’ (Bateson et al., 2012, p.152). US- and UK-based research illustrates that older individuals have consistently low rates of condom use, and lower rates of condom use than younger age groups (Foster et

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al., 2012; Gott, 2005; Reece et al., 2010; Sanders et al., 2010; Schick et al., 2010).

Patterns of condom use are gendered. An Australian study of 2,438 individuals aged 50 or older presenting at a sexual health clinic found that men (54%) were much more likely than women (19%) to report condom use in the past three months (Bourne and Minichiello, 2009; see also Reece et al., 2010). Altschuler and Rhee (2015) argue that women's ability to negotiate condom use is closely tied to relationship power and self-esteem, 'with women who do not experience or command enough power in their relationships not insisting on condoms' (p. 301). Some women in Altschuler and Rhee's study were also met with violence or anger from male partners after requesting that they use a condom. Thus, older women's 'risky' sexual practices must be understood within a context of disparate gendered power relations, *in conjunction with* the systematic devaluing of older adults. In contrast, research from the UK (Gott, 2001, 2005) and the US (Foster et al., 2012) found that older men were more likely to engage in risky sexual practices than women.

Participants in Fileborn and colleagues' (2017a) study reported using a range of safer sex practices in addition to or instead of condoms. These included:

- Being in a monogamous relationship;
- Talking to their partner about their sexual history;
- Having an STI test, and;
- Engaging in lower-risk sexual practices (e.g., non-penetrative sex).

However, these strategies were not consistently used in all contexts where there was some likelihood of STI transmission. As with condom use, rates of STI testing in older cohorts also appear to be low (Schick et al., 2010).

Gott's (2001) UK-based research indicates that some older adults engage in risky sexual behaviour—in this case defined as inconsistent condom use despite having more than one sexual partner in the past five years—with 7% (n = 21) of participants (n = 319) falling into this category. Widowed heterosexual men who use erectile-enhancing medications are also more likely to engage in risk-taking sexual behaviour, as well as having greater opportunity to meet new sexual partners (Smith and Christakis, 2009). Delays in help-seeking behaviour and STI testing can result in older adults presenting with more severe symptoms, while ageist assumptions regarding older adults as 'asexual' can contribute towards delays in diagnosis or misdiagnosis (Minkin, 2010; Wilson, 2006). This is further compounded by the fact that some of the common symptoms of STIs and HIV overlap with common 'symptoms' of ageing (Nash et al., 2015).

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Together, this body of research suggests that older individuals who are ‘at risk’ of contracting an STI (i.e., those entering new relationships, dating casually, or with multiple sexual partners) may require support from healthcare professionals. As Minichiello and colleagues (2004, p. 125) note, ‘it is not age that decreases or increases risk [of STIs], but sexual practices’, suggesting that we must strive to be inclusive of sexual health needs across the life-course.

Knowledge of and attitudes about safer sex

Typically, older individuals did not receive comprehensive sexualities education at school. While the extent to which sex education was provided is contested, and historical work suggests that *some* sex education was generally provided (Carter, 2001; Cook, 2012), on the whole we cannot assume that older individuals have received extensive opportunities to learn about safer sex and sexual health (Fileborn et al., 2016b; Ross et al., 2013; Smith and Schmall, 1983). Even for those who did receive sexuality education when younger, this information may now be outdated or forgotten (Smith and Schmall, 1983).

Although a small number of sexuality education programmes targeted towards older adults have been developed (e.g., Garrity, 2010), contemporary sexualities education, safer sex campaigns, and sexual health policy are almost exclusively targeted towards younger people (Bodley-Tickell et al., 2008; Bourne and Minichiello, 2009; DeLamater, 2012; Gott, 2001, 2005; Kirkman et al., 2013; Kirkman et al., 2016). Conversely, ageing policy rarely considers the sexual health and wellbeing needs of older adults (DeLamater, 2012). This is further fuelled by the assumption that older individuals are ‘asexual’ or ‘past it’, and thus do not require information on sexual health (Altschuler and Katz, 2015; Kirkman et al., 2016; Ross et al., 2013). Older adults rely on sources including the Internet, media, and healthcare providers (Fileborn et al., 2016b; Slinkard and Kazer, 2011) to find information about sexual health. However, Australian research suggests that seeking such information is not common (Fileborn et al., 2016b).

There is evidence that older adults have some gaps in their knowledge on safer sex (Lyons et al., 2017; Ross et al., 2013; Smith and Schmall, 1983). For instance, participants in a qualitative Australian study tended to overemphasize the use of condoms as constituting ‘safer sex’, and were less likely to discuss strategies such as having an STI test and engaging in lower-risk sexual practices (Fileborn et al., 2017a). Older individuals may overestimate the level of protection provided by condoms, and have lower knowledge of how certain STIs, e.g. chlamydia, gonorrhoea, and genital warts, are transmitted (Lyons et al., 2017). Canadian research with 202 women aged 50 and older found that participants had ‘moderate levels of knowledge pertaining to general sexual health issues’, with slightly lower levels of knowledge on HIV/AIDS specific issues (Ross et al., 2013, p. 171; see also Foster et al., 2012). Knowledge about STIs and

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safer sex is gendered, with women typically having better knowledge than their male counterparts (Lyons et al., 2017).

Challenges or barriers to safer sex

The limited research on older adults' use of safer sex practices suggests that they can face a range of barriers to having safer sex. Recent Australian research (Fileborn et al., 2017b), for example, illustrated that commonly encountered barriers included:

Embarrassment: some older individuals were too embarrassed to discuss the need to use condoms or other types of safer sex.

Stigma: the need to use safer sex practices was associated with 'loose', 'promiscuous', or 'dirty' individuals. Stigma could make it difficult to discuss safer sex with a partner, for fear of offending them or implying that they must be 'promiscuous'. Gender also comes into play here, with women subject to negative responses and judgment more so than their male counterparts (as noted earlier). US research indicates that stigma is also shaped by race, with Lichtenstein (2008) reporting that African-American elders were more likely to perpetuate STI-related stigma than white participants—a phenomenon which is itself embedded in histories of racism and discrimination, and the social construction of black elders as 'morally upstanding'. Adherence to STI-stigma was also associated with 'desires to delay or avoid treatment for STIs' (Lichtenstein, 2008, p. 111).

Erectile difficulties: some older men were reluctant to use condoms, as doing so would result in them losing their erection.

Lacking the requisite skills and safer sex culture: many participants had grown up in the pre-AIDS era where comprehensive sex education not was provided, 'safe sex' tended to refer to pregnancy prevention (see also Bodley-Tickell et al., 2008; Fileborn et al., 2016a; Nash et al., 2015; Spring, 2015), and safer sex was not seen as relevant to long-term, monogamous relationships. As a result, some older adults may lack confidence and skills in using different safer sex practices (see also Foster et al., 2012), negotiating the use of safer sex practices (see also Bateson et al., 2012; Bourne and Minichiello, 2009; Smith et al., 2010), or may not incorporate safer sex as a routine part of their sexual lives (see also Spring, 2015).

Reduced pleasure: the perception that condoms reduced physical sensation was a disincentive to their use. Condom use could also be painful for older women who experience vaginal dryness.

Key points

- STI rates are increasing among older adults.
- Older adults can face a range of barriers to safer sex practices, and use them inconsistently.
- Some older adults have substantial gaps in their knowledge of STIs and safer sex practices.

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Sexual violence in later life

For the purposes of this chapter, we take a broad and inclusive approach to defining sexual violence. This is appropriate, given that we draw on research that stems from different legal jurisdictions, and studies that operationalize different definitions of sexual violence. We use the terms sexual violence and sexual assault interchangeably, and take these to refer to the same spectrum of behaviours. The World Health Organization (Krug et al., 2002, p. 149) defines sexual violence as:

Any sexual act, attempt to obtain a sexual act, unwanted sexual comments or advances, or acts to traffic, or otherwise directed, against a person's sexuality using coercion, by any person regardless of their relationship to the victim, in any setting.

Coercion is taken here to 'cover a whole spectrum of degrees of force' beyond physical violence to include 'psychological intimidation, blackmail or other threats ... [or when] the person aggressed is unable to give consent' (Krug et al., 2002, p. 149). Any older person can experience sexual violence. Likewise, it can occur in various relationship contexts, including same-sex relationships. Women can perpetrate this violence, albeit significantly less commonly than men. To date, the majority of research has focused on the experiences of older, heterosexual women.

Prevalence

International research indicates that sexual violence against older adults is relatively uncommon. For example, Bows and Westmarland's (2017) examination of police data in the UK revealed that those aged 60 and over constituted 0.6% of recorded rapes, and 1.4% of sexual assaults by penetration. Bows' (2017b) recent review of this issue found that estimates of sexual violence against older adults in the past 12 months ranged from 0.2%–8%, with these figures varying substantially across studies from different disciplinary and methodological approaches. While older men can be the victims of sexual violence, older women are disproportionately impacted. That is, as with sexual violence at other points in the life-course, sexual violence against older adults is a highly gendered occurrence (Bows, 2017a; Bows and Westmarland, 2017).

However, barriers to reporting and recording sexual offences complicate these findings. Older individuals, particularly those who reside in residential aged care facilities, are routinely excluded from surveys on sexual violence (Fileborn, 2016). Internationally, sources of large-scale data collection on sexual violence often have cut-off ages that exclude older cohorts (Bows, 2017a, 2017b; Bows and Westmarland, 2017; Fileborn, 2016). Different studies draw on diverse definitions of what constitutes sexual violence and, for that matter, 'older age' (Bows, 2017b; Fileborn, 2016). Much of the work done on this topic draws on different disciplinary perspectives, making it difficult to compare findings across this body of work (Bows, 2017a, 2017b; Fileborn, 2016).

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It is questionable to what extent older adults themselves understand and identify experiences of sexual violence. For example, older individuals may not recognize or label sexual violence when it occurs in the context of marriage or a long-term relationship (Fileborn, 2016; Mann et al., 2014; Vierthaler, 2008). It is important to recognize that older adults may downplay or minimize their experiences. Older adults with cognitive impairments may be particularly vulnerable to sexual assault, as they may have difficulty explicitly and verbally disclosing their experience (Fileborn, 2016; Mann et al., 2014; Speck et al., 2013).

Myths and stereotypes about sexual violence can also obscure older adults' experiences (Bows and Westmarland, 2017; Fileborn, 2016; Vierthaler, 2008). One such misperception is that sexual assault only happens to 'sexually desirable' or attractive young women, with older women falling outside of this category (Bows and Westmarland, 2017; Fileborn, 2016; Vierthaler, 2008). Indeed, the construction of older women as 'asexual' and undesirable renders them as supposedly unlikely targets for sexual violence (Bows and Westmarland, 2017; Fileborn, 2016). However, this assumption perpetuates the myth that sexual violence occurs because of men's 'uncontrollable' sexual desire, rather than as an act steeped in gender-based power and control (Bows and Westmarland, 2017; Fileborn, 2016). Bows and Westmarland (2017) illustrate how a range of myths and stereotypes has likewise developed about sexual violence against older adults. For instance, 'real' rape against an older person is typically depicted as involving a stranger, as taking place at night, and as occurring in the course of another criminal offence being committed, such as burglary. Further, they argue that older victims are constructed as being especially vulnerable *because of* their age and assumed physical frailty, regardless of whether this was actually a contributing factor. However, while it is undoubtedly problematic to construct older adults as vulnerable to sexual violence solely because of their physical frailty, we suggest it is equally unhelpful to ignore or downplay the material realities of older bodies and the ways in which these may shape older adults' experiences and the impacts of sexual violence. Indeed, some scholars have argued that the physical vulnerability of older adults may place them at increased risk of sexual violence, as some perpetrators may specifically target older adults *because of* this perceived or actual vulnerability (Vierthaler, 2008).

Together, the factors discussed here suggest that current prevalence estimates of sexual violence in later life likely underestimate the extent of this issue.

Sexual violence across the life-course

When considering the sexual assault of older adults, particularly older women, it is important to locate these experiences within a life-course perspective. While the research discussed earlier illustrates women's

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experiences in later life, women (and men) may have experienced sexual assault in childhood, adolescence, and across their adult years.

Globally, the World Health Organization estimates that one in three women and girls will experience some form of physical or sexual violence in their lifetime (WHO, 2013). Additionally, one in five girls and between 5–10% of boys are estimated to have experienced sexual violence in childhood (WHO, 2016). Women in particular may experience multiple forms of sexual violence across their life-course. Same-sex attracted and gender-diverse people experience sexual violence at similar, if not higher, rates to those of heterosexual, cisgender women (Fileborn, 2012). Again, there is very little research examining the impacts of these earlier experiences in later life. However, the work that has been done suggests that sexual assault in earlier life may resurface in later years in the following ways (see Clark and Fileborn, 2011):

- Disclosing experiences of sexual violence earlier in life for the first time
- Reliving or having ‘flashbacks’ to earlier experiences of sexual violence, especially those living with dementia or other cognitive impairments
- Aged care and other healthcare facilities can replicate the power dynamics of abuse (e.g., by removing individual control and autonomy), which may be triggering or re-traumatizing for victim-survivors

Aged care professionals should therefore be mindful of the fact that a substantial minority of older individuals will have experienced sexual violence at some point in their lives.

Offending contexts and offenders

Older adults experience sexual violence across a range of different locations and relationship contexts (Bows, 2017b; Fileborn, 2016; Mann et al., 2014). As is the case with sexual violence more generally, the vast majority of perpetrators against older adults are male (Bows, 2017b; Bows and Westmarland, 2017). In their analysis of UK police data, Bows and Westmarland (2017) found that perpetrators were typically younger than their victims. Perpetrators generally know their victims, and this is again consistent with sexual violence across the life-course (Bows and Westmarland, 2017). Perpetrators are most commonly partners or ex-partners, other family members, friends and acquaintances, carers (including informal and unpaid carers, and professional service providers), co-residents in residential care settings, and, less commonly, strangers (Bows, 2017; Bows and Westmarland, 2017; Mann et al., 2014). Sexual assault against older adults occurs across a range of different locations, most commonly in residential settings (such as the victim’s or the perpetrator’s home), or within residential and other care facilities (Bows, 2017b; Bows and Westmarland, 2017).

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Impacts of sexual violence

Sexual violence can have a range of physical, psychological, emotional, and social impacts on victim-survivors (Boyd, 2011). Some of these impacts are common to victim-survivors generally, while others are more specific to older victim-survivors. The impacts of sexual violence can occur in the immediate aftermath of an incident, and can also persist in the medium to long term (Boyd, 2011). The particular impacts experienced and their severity varies across individual victim-survivors, and are shaped by contextual factors surrounding the assault (Boyd, 2011; Ullman and Brecklin, 2003). For instance, older women who have experienced multiple forms of violence across their life may have more pronounced and longer-term impacts. However, some authors have argued that older women may experience more intense impacts (Bows, 2017a; Burgess and Morgenbesser, 2005).

Across the research, common identified impacts of sexual violence include (Bows, 2017a,b; Boyd, 2011; deVisser et al., 2007; Ullman and Brecklin, 2003):

- Psychological and emotional impacts:
 - Depression
 - Anxiety
 - Suicidal ideation and/or attempts, and self-harm
 - Fear
 - Memory problems, particularly relating to details of the incident(s), confusion
 - Post-traumatic stress disorder (PTSD)
 - Drug and alcohol abuse/misuse
 - Lower self-esteem
 - Difficulty sleeping, nightmares
 - Crying
 - Becoming withdrawn
 - Distress and changes in 'usual' behaviour patterns. This may be especially relevant for victims who experience cognitive impairments. Distressed behaviour may be particularly prevalent during personal care, such as assistance with showering and toileting, or exhibited towards men
- Physical impacts:
 - Genital injury—to which older women may be more prone (Poulos and Sheridan, 2008)
 - Incontinence
 - Loss of appetite

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- Physical injuries, such as bruising, cuts, broken or fractured bones. However, it is important to note that physical injuries only occur in a minority of sexual assaults
 - STIs and HIV
 - Increasingly impaired physical health and illness, including increased mortality (Ullman and Brecklin, 2003; Cook et al., 2013; Speck et al., 2013). This may be enhanced for women who have experienced multiple forms of abuse, or prolonged abuse, across their life
- Social impacts:
 - Withdrawing from friends and family
 - Decreased interest in or fear of engaging in consensual sexual activity, no longer enjoying consensual sex, finding sex painful (dyspareunia)
 - Avoiding social situations
 - Difficulty with trust and intimacy

Professionals working with older clients should be aware of these impacts, which may serve as indicators that someone has experienced sexual violence.

Identifying and responding to sexual assault

There is a dearth of awareness of the specific support needs of older adults who have been sexually assaulted, or regarding what constitutes 'best practice' in identifying and responding to older sexual assault victims (Bows, 2017a; Fileborn and Barrett, 2019; Mann et al., 2014). In this section, we address the small body of research on responding to older victim-survivors, and draw more broadly on research regarding the support needs of victim-survivors.

Recent research suggests that aged care service providers and other professionals can face barriers in recognizing when sexual violence has occurred, and in providing an appropriate response to the victim-survivor. Fileborn and Barrett's (2019) research with aged care service providers identified a range of barriers to implementing best-practice responses, including:

- Lack of institutional policy for how to respond
- Limited knowledge of what constitutes sexual assault (see also Vierthaler, 2008)
- Lack of training on how to respond appropriately
- Defensive responses from family members and/or alleged perpetrators
- Poor or non-existent relationships with support and counselling services. Recent UK-based research with sexual assault professionals

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found that they had minimal experience responding to older victim-survivors, suggesting that this group may not be accessing appropriate support (Bows, 2017a)

- The victim-survivor being unable to verbally communicate what has happened (e.g., due to cognitive impairment; see also Bows, 2017a). Some were also unable or unwilling to disclose, for example, due to embarrassment or shame (see also Bows, 2017a)
- The victim-survivor being in poor health, which may decline further post-assault (see also Bows, 2017a)

Bows' (2017a) work with sexual assault professionals likewise identified a range of challenges in providing support to older victim-survivors. These included physical challenges related to the victim-survivor's poor health or mental and physical impairments, similar to that discussed earlier. For Bows' participants, health-related challenges could also pose practical barriers in terms of performing forensic examinations, or for survivors being able to physically access and attend support services.

Evidence suggests that criminal justice professionals such as the police can also respond in problematic ways to older victim-survivors. Most victim-survivors never report their experience to the police, and this is also the case for older people (Connolly et al., 2012; Mann et al., 2014). The limited evidence available on older victim-survivors suggests that when they do report to the police, their cases are less likely to proceed to prosecution. Cognitive function may also play an important role, with research by Burgess and Phillips (2006) finding that sexual assault cases where the older victim had dementia were *less* likely to proceed to prosecution in comparison to older victims without dementia. This is concerning given that older individuals with cognitive impairments may be especially vulnerable to sexual assault (Payne, 2010). Payne (2010) found that cases involving cognitively impaired victims usually required another witness to the assault in order for the case to progress through the justice system, as victims with cognitive impairment may be unable to provide verbal evidence of what has happened (and, we would add, police are likely inadequately trained in communicating with older people with cognitive impairment). However, police and criminal justice system responses to the sexual assault of older individuals is another area that remains largely under-researched: we know little about the experiences of older victim-survivors who report to police, nor about the attitudes of police and criminal justice workers to older victim-survivors and the extent to which these may be shaped by ageist assumptions (Fileborn, 2016; Payne, 2010).

More general research on sexual assault disclosure has found that inappropriate responses to disclosures can also include (Ullman, 2010):

- Expressing disbelief or dismissing the victim's experience
- Blaming the victim for what happened

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- Excusing or downplaying the actions of the perpetrator
 - Reporting the experience to others without the victim's consent
- However, there is an important exception here for older adults with mental or cognitive impairments who may be unable to disclose by themselves. In some jurisdictions, healthcare professionals have a legal obligation to report sexual assault that has happened to individuals in their care, and readers should familiarize themselves with relevant legal requirements in their country
- Shifting the focus away from the victim-survivor, e.g., to the emotional response of the disclosure recipient. This is often termed an 'ego-centric' response

It is vital that those who receive a disclosure or become aware that sexual violence may have occurred respond appropriately. The response received can play a substantial role in victim wellbeing and recovery, and in their likelihood to seek further support (Ullman, 2010). The following factors tend to be associated with 'positive' and best-practice responses to sexual violence (Fileborn and Barrett, 2019; Ullman, 2010; Vierthaler, 2008):

- Believing the victim and taking their experience seriously
- Listening to the victim
- Offering tangible support and information, such as putting the victim-survivor in contact with a counselling service
- Avoiding intrusive questioning or 'detective' work. However, the use of gentle, open-ended questions giving the victim space to share their experience in their own words is often appropriate
- Affording the victim control over what happens next (again, with the exception of mandatory reporting requirements)
- Having clear policy and procedures in place in institutional or organizational settings
- Establishing trust and a sense of safety with the victim-survivor
- Being attuned to the victim-survivor's 'usual' behaviour, so that any changes are readily noticed. This may be particularly important for victim-survivors with cognitive or other impairments
- Collaboration and establishing professional relationships between aged care service providers and sexual assault support professionals
- Provision of education and training on sexual violence to aged care and other health professionals. Conversely, sexual violence support workers may benefit from training on elder abuse and other issues related to ageing

Key points

- Sexual violence against older adults appears to be relatively uncommon. However, barriers to reporting and disclosure mean that the true extent of violence is hidden.

- Sexual violence against older adults occurs across various relationship and offending contexts.
- Older individuals with physical and/or cognitive impairments may be particularly vulnerable to sexual violence.
- Sexual violence has short- to long-term impacts on older adults, including physical, psychological and social impacts.
- Aged care and healthcare providers face barriers to identifying and responding appropriately to sexual violence.
- Aged care and healthcare providers require training, and the implementation of organizational policy, to support best-practice responses to sexual violence.

Sexual consent and partner communication

In discussing sexual violence and older adults, it is important to consider the issue of sexual consent. Indeed, consent is often the key factor that distinguishes sexual violence from wanted, agreed sexual encounters. Effective sexual communication—or how we talk to our partners about our sexual wants, needs, and desires—is central in ensuring that sex is consensual, but also in maximizing the likelihood that partnered sex will be mutually pleasurable and fulfilling. Sexual communication has implications for sexual health, for example, being able to effectively discuss and negotiate condom use will in turn shape the likelihood of STI transmission. However, as with many other aspects of older adults' sexual relationships, sexual consent and communication remain highly under-researched. As a result, we know very little about how older adults understand the concept of sexual consent, or how they negotiate consent and pleasure within their sexual relationships.

Sexual consent can be conceptualized in a range of different ways, and has both legal and common-sense definitions. Legal definitions of what constitutes consent, and what needs to have taken place to show that consent was given, vary substantially across jurisdictions. Legal understandings of sexual consent are often not aligned with what sexualities scholars might consider 'best practice' in negotiating sexual consent: legally 'consensual' encounters are not always the same as 'ethical' ones (Gavey, 2005). We outline some criteria for considering whether a sexual encounter has been negotiated in, or consented to, in an 'ethical' manner later in this discussion.

Potential barriers to negotiating sexual consent

Older individuals can face a range of barriers to effectively and openly negotiating sexual consent and pleasure in their relationships. Some of these barriers are encountered across all age groups, while others relate more specifically to older cohorts.

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As we alluded to in the previous section, understandings of sexual consent have shifted historically and across different social and cultural contexts (Gavey, 2005). For example, a man's sexual access to his wife was once legally enshrined (and continues to be in many countries outside of the global north), meaning that sexual consent was implied and ongoing within a relationship, rather than something to be negotiated on a continual basis. Outdated notions of sexual consent presumed that the absence of a verbal 'no' was sufficient to indicate consent, rather than consent requiring active and willing participation (sometimes referred to as 'affirmative consent'). Heterosexual sexual scripts—that is, the rules or norms that tend to govern how our sexual encounters unfold—have often been based on the stereotype of men as active pursuers of sex, while women will initially resist and then acquiesce to sex but never actively initiate it themselves (Allen, 2004; Gavey, 2005). Such scripts tie into problematic misconceptions, such as that women say 'no' when they really mean 'yes', which can act as barriers to clear and effective sexual communication. For gay men, there is often the assumption that they are always 'up for' sex, making sexual refusal challenging.

Many of us are resistant to verbally discussing sexual consent and sexual pleasure with partners (Burkett and Hamilton, 2012). Often, this is based on the notion that sex and consent should not require verbal discussion. This is related to the pervasive cultural belief that discussion (for example, asking your partner to use a condom) disrupts the 'natural' flow of sex. Rather, we should 'just know' what our partners want, or believe that subtle bodily cues are sufficient in communicating consent and pleasure. While body language and other nonverbal cues are an important aspect of sexual communication, they are not always sufficient as a form of communication by themselves (Cowling and Reynolds, 2004).

Embarrassment and stigma also play a role. Many of us find it difficult to talk openly about sex and sexual pleasure, given that sex remains a largely taboo topic in many cultures. This embarrassment and stigma is likely heightened for women who grew up in a social context where they were often not supposed to enjoy or actively want sex: it is difficult to express our sexual desires if those desires are not supposed to exist, or are framed as aberrant if they do (Allen, 2003). Relatedly, this may cause challenges in communicating to a partner what we 'want' or enjoy sexually. While this challenge may be experienced by people of all ages and genders, it is likely to be particularly acute for older women (and 'sexual dissidents' such as same-sex attracted people) who may have been inculcated with the message that sex and sexual pleasure are 'wrong' and 'dirty' when growing up, and may have been discouraged from engaging in practices such as masturbation (Fileborn et al., 2015a, 2015b), which play a central role in exploring our own sexual desires and what 'works' for us in providing sexual pleasure. Men can face the pressure to have 'mastered' sexual skills, making any discussion of technique or what a sexual partner wants or enjoys an affront to their masculinity and a potential source of embarrassment.

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These gendered dynamics are also relevant when considering the potential consequences of sexual communication. Older women in Fileborn and colleagues' (2017a) qualitative research reported that they were reluctant to refuse sex without a condom out of concern that their partner would leave them for someone else who would have condom-less sex. It is certainly plausible that similar pressures would be experienced when it comes to refusing sexual activity, particularly when coupled with some of the sexual scripts discussed earlier that depict women as the passive recipients of sex. Australian research suggests that heterosexual male partners do not always respond 'well' to women's attempts to discuss their sexual pleasure and partnered practices. Some women in Fileborn and colleagues' (2015a) research, for example, reported that their male partner became angry and defensive when they tried to initiate conversation about their sexual technique, particularly if they adhered to the belief that 'real' sex required penetrative intercourse.

General principles of 'good' communication and negotiating consent

Much of the research on ethical sexual practices has focused on adolescents and young adults. Nonetheless, there are some valuable lessons from this work that will also apply to older adults. Rubin (1992, p. 110) argues that, in fostering ethical sexual practices, our focus should be placed on 'the way partners treat one another, the level of mutual consideration, the presence or absence of coercion, and the quantity and quality of pleasures they provide'. Carmody relatedly asserts that, 'all sexual encounters, regardless of the gender of the people involved, invite the possibility of ethical or unethical sexual behaviour' (2003, p. 201). Both Rubin's and Carmody's approaches to the ethical negotiation of sexual encounters focus on the extent to which the encounter is actively wanted, pleasurable, and enjoyed by both/all parties, rather than certain types of sexual practices and relationships being constructed as 'good' or 'bad' (e.g., anal sex, sex with multiple partners, same-sex relationships, particularly as compared to more 'normative' practices such as monogamous partnerships and penetrative, heterosexual sex). There is no one 'correct' way to communicate and negotiate sexual encounters under such a model. Rather, we must be attentive to the diverse range of ways our sexual partners may indicate their willingness to participate in a sexual encounter, as well as the pleasure they experience (or not).

There are many contextual factors to take into account in considering whether a sexual encounter has been negotiated in an ethical way. While we cannot cover these exhaustively in this chapter, based on the work of Carmody (2009), some key factors include:

- Gendered and other power differentials. For example, is it possible that one partner feels subtly pressured to engage in sex (perhaps they fear their partner will leave them if they refuse, as highlighted earlier)? Is one partner in a position of power over the other, such as an employer/employee? The existence of such power differentials does not mean that ethical, consensual sex *cannot* take place. However, they

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do require careful negotiation, particularly on the part of the person in a position of greater power

- Was sex and pleasure actively discussed? However, this should also take into account the diverse ways in which we communicate (e.g., body language, vocal tone, etc.)
- Was the use of condoms or other safer-sex practices discussed? Did all individuals involved feel able to openly raise issues about safer sex?
- Was there space for sex to be refused?
- Were all partners attentive to any signs that someone might be uncomfortable, disinterested in, not consenting to, or not enjoying a sexual encounter? Did they 'check in' with a partner if this was the case?
- Was the context of the sexual encounter taken into account? For example, what quantity of alcohol or other drugs had been consumed? Had anything else happened that might have impaired a partner's capacity to give free and full consent? Might someone feel afraid or unable to say no?
- Did each person involved in an encounter express concern for the physical and emotional safety and wellbeing of their partner, and themselves (that is, did they engage in self-care)?

Consent and dementia

When it comes to sexual consent and older adults, a key consideration is the capacity of those with dementia or other forms of age-related cognitive impairment to meaningfully consent to sex. This is a hotly contested issue, and one for which there are no straightforward answers or solutions. A delicate balancing act is required in ensuring that those living with dementia are protected from sexual harm and abuse (particularly given that people living with dementia may face a higher risk of sexual assault, as discussed earlier), while also ensuring that the sexual rights of the individual are upheld (Bauer et al., 2013; Fileborn 2016; Tarzia et al., 2012).

Living with dementia does not automatically mean that someone is incapable of giving sexual consent, although it may shape the *contexts* in which consent can be given. However, in practice it can be difficult to determine whether an individual is able to consent at any given time, particularly as the cognitive decline associated with dementia is not always linear, and individuals may have moments of lucidity (Archibald, 2002; Fileborn, 2016). Conversely, we must also remain cognizant of the sexual behaviours of older adults living with dementia, and the impact they may have on others. For instance, several qualitative studies (Mann et al., 2014; Fileborn and Barrett, 2019) have documented older women being 'badgered' for sex by male partners living with dementia, with the men unaware of the extent of their demands. In some instances, men with dementia continue to be prescribed erectile-enhancing medications,

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contributing towards their (unintentional) harassment of partners. Clinicians in a position to prescribe erectile-enhancing medication to older men with dementia or other cognitive impairments should discuss this with the man's partner if possible.

Key points

- Older adults can encounter barriers to negotiating sexual consent and talking about sex with a partner, including norms about how sex is 'done', gendered power differentials, and shame and stigma associated with sex.
- Ethical sexual encounters focus on the extent to which sex was wanted, free from coercion, and mutually pleasurable.
- Dementia can make it difficult to determine if someone has capacity to consent to sex. However, the sexual rights of an individual living with dementia should be promoted where possible, provided that the potential for abusive or coercive sexual encounters is minimized.

Sexual difficulties in later life

As indicated already, various sexual difficulties can be experienced by older adults. A recent literature review identified that for women the main age-related sexual difficulties were vaginal dryness and discomfort and a lack of interest in sex (Træen et al., 2017b). For men, the main difficulties were erectile dysfunction, low sexual desire, and inability to orgasm (Træen et al., 2017b). While not all older adults will experience a sexual difficulty, the frequency of problems related to sexual desire, orgasm, and sexual function increases with older age (Carpenter and DeLamater, 2012).

Research consistently reports that there is a connection between poor health and sexual difficulties (Træen et al., 2017b), and in particular medical comorbidities (Gewirtz-Meydan and Ayalon, 2016). This could be due to the disease/illness itself, psychological factors connected with it, or indeed the drugs that are used to treat or manage the condition. Many medications prescribed for health problems, including long-term conditions that are more likely to be diagnosed at midlife, have sexual side-effects. For example, some antihypertensive drugs are associated with delayed or absent orgasm in women, and ejaculation dysfunction (dry orgasm) in men (Dean, 2015).

Many of the drugs prescribed to manage mental ill health can induce or exacerbate sexual dysfunctions. For example, SSRIs to treat depression can cause erectile difficulties, lack of interest in sex, and inability to orgasm, and tricyclic antidepressants, which are also used to manage pain, can interfere with the ability to orgasm in both women and men (Wood and Runciman, 2015). Psychotropic drugs that can cause sexual

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dysfunction include paliperidone, haloperidol, and aripiprazole (De Hert et al., 2011). Dean (2015) cautions that the various ways of managing drug-related sexual difficulties, such as reducing the dose or substituting the drug, can be risky (e.g. relapse of the condition). Clearly, the treatment and prevention of drug-related sexual difficulties must be balanced against the effective treatment of the condition.

Sexual difficulties are common in patients with a psychiatric diagnosis and relate to various, potentially overlapping, factors, including the illness, physical illness, substance abuse, and medications (Balon, 2015). There is a connection between depression and decreased sexual desire, although we know that antidepressant medicines can also cause this and other sexual difficulties (Balon, 2015). Patients diagnosed with bipolar disorder can experience either 'hypersexuality' or low sexual desire (Balon, 2015). Increased sexual difficulties have been found in people with anxiety-related disorders (Balon, 2015). Research has shown that women and men with schizophrenia report high levels of sexual dysfunction when compared to the general population (Hallett and Rees, 2017). A common dysfunction reported in schizophrenia is decreased sexual desire, although some patients show signs of excessive masturbation (Balon, 2015).

Again, there are usually multiple contributory factors to sexual dysfunction in patients with mental ill health (Dean, 2015; Balon, 2015). As well as those indicated previously, social and interpersonal factors, e.g. relationship quality, sexual performance of the partner, body image, previous sexual trauma, can influence sexual desire, interest, and pleasure (Heiman, Long et al., 2011; Hinchliff, Gott and Ingleton, 2010). But it is important to note that sexual difficulties may not be a cause for concern. Indeed, clinicians should ask this question as many people report a sexual difficulty but do not experience it as a problem (Træen et al., 2017b). There is research evidence which highlights that women who have sex with women manage sexual difficulties better than women in sexual relationships with men (Winterich, 2003). Reasons include their wide repertoire of sexual activity, which is not focused predominantly on penetration, and equal gender relations that enable the negotiation of sexual acts. Taking a sexual history (see the next page: Guidance for health professionals to improve their sexual communication) helps professionals to ask the necessary questions, including about sexual orientation, identify potential factors that interfere with sexual function, and determine the way forward.

Key points

- There is an increased chance of experiencing a sexual difficulty at middle and later life.
- Sexual difficulties can be caused by biological, psychological, or social (interpersonal) factors.

- Medications used to treat health conditions and mental ill health can have serious sexual side effects.
- Not all sexual difficulties are a source of distress to the patient.

Sexual communication between health professionals and older patients

Despite the areas of need outlined throughout this chapter, there is consistent evidence that health professionals tend not to ask older adults about sexually related matters. The reasons vary, and we explore them here. But first it is interesting to note that research conducted in the area of healthcare and older adults' sexual health and sexual wellbeing indicates interesting differences in the perspectives of health professionals and older adults themselves. Quite simply, many older adults report that they want the health professional to ask them about sex, whereas health professionals think that patients should be the ones to raise the topic.

This finding holds particular relevance in the area of psychiatry, where psychiatrists have been found to underestimate the extent to which their patients experience a sexual difficulty. Indeed, Dossenbach and colleagues (2005) examined the prevalence of sexual difficulties in patients with schizophrenia (based on patient reports and psychiatrists' perceptions) and found that psychiatrists underestimated the sexual difficulties their patients could experience; a finding which was statistically significant (at $P < 0.0001$) and internationally relevant (across 27 countries).

Many studies report that older adults want their doctors to be proactive when it comes to sexual health (Bedell et al., 2002; Laumann et al., 2009; Lindau et al., 2007; Moreira et al., 2006; Sarkadi and Rosenqvist, 2001; Warner et al., 2008). But health professionals often think differently, and studies have identified that doctors are rarely proactive with their older patients. For example, they may not provide information about how a health condition can affect sexual function (Bedell et al., 2002; Sarkadi and Rosenqvist, 2001), provide details about STIs after patients have consulted a genito-urinary medicine clinic (Gott, 2001), or offer relevant tests, such as HIV, even when this is suggested by the patient (Lindau et al., 2007). When patients have sought help from their GP for sexual difficulties, there are reports of the GP not being helpful, including not offering treatments such as erection-enhancing medicines in the context of prostate cancer, or not answering patients' questions about sexual problems (Hinchliff et al., 2017; Rutte et al., 2016).

One recent study tested physician (the majority, 77.1%, were general practitioners) responses to a hypothetical male patient who was presenting with occasional erectile difficulties that had a clear

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psychosocial aetiology (Gewirtz-Meydan and Ayalon, 2016). Conducted in Israel, two identical vignettes were used, which differed only by the age of the patient: one was aged 28 years, the other aged 78 years. The results highlighted an age bias in terms of how the physicians diagnosed the men. For example, the younger man was more likely to be diagnosed with performance anxiety, and the older man erectile dysfunction. The older man's problem was more likely to be viewed as caused by health issues, hormone changes, and lowered sexual desire. He was more likely to be referred to urology, and advised pharmaceutical treatment such as testosterone replacement therapy and PDE5 inhibitors (e.g. sildenafil). The younger man was more often referred to a sexologist. The authors concluded that the young man received an overall more positive prognosis.

Bouman and Arcelus (2001) also identified differences in the ways in which psychiatrists responded to young and old male patients. They examined the attitudes of UK-based psychiatrists who specialized in either in general psychiatry or late-life psychiatry, and found that the psychiatrists were more likely to refer older patients with a sexual problem to community psychiatric nurses (CPNs), whereas younger (middle-age) patients were referred to sex therapy. Referring patients to CPNs was identified as inappropriate by the authors as CPNs do not receive training in sex therapy. Thus, the referred patients would not receive adequate treatment for their sexual problems. They also identified that both groups of psychiatrists were less likely to take a sexual history of older male patients than they were of younger patients, indicating that it was not appropriate to do so.

The reasons why health professionals do not always manage the sexual healthcare needs of older patients correctly are varied. Barriers that health professionals face include: stereotypes of older age, such as believing that older adults are not sexually active (Gott et al., 2004; Pascoal et al., 2017), or that it is a private topic that the older patient would not wish to discuss (Gott et al., 2004); the older person being seen as a parental figure (Wei and Mayouf, 2009); and the older-old, in that the older the patient, the less likely a physician would raise the issue of sex (Pascoal et al., 2017). Lack of time during consultations and inadequate knowledge of the issues that can affect the sex lives of older adults and their treatments have also been identified (see Hinchliff and Gott, 2011). Health professionals may be pessimistic about the effectiveness of treatments for sexual difficulties: an issue identified more widely in psychological and psychiatric services, and related to the societal assumption that older adults tend to hold negative attitudes (Knight et al., 2003).

In a review of the empirical literature, Hinchliff and Gott (2011) identified that many older adults who had a sexual problem did not seek help. One study in Korea found the 96% of women and 92% of men who reported a sexual problem had not sought professional help but had spoken with friends, family, or partners about it (Moreira et al., 2006). And a UK study

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identified that 40% of the sample of older women and men with sexual concerns had not sought professional help (Gott, 2001). Similarly, Rutte and colleagues (2016) found that 69% women and 68% men with type 2 diabetes who lived in the Netherlands experienced sexual difficulties, but not all were aware of the connection between diabetes and sexual difficulties. While few had looked for help for their sexual problem, men were more likely to have done so and this was from their GP. Believing they would be dismissed or receive an 'ageist response' were reasons given by older (heterosexual) Australian participants for not raising the issue of sex with their health professional (Fileborn et al., 2017b). Other barriers to seeking professional help include accessibility of the health setting, patient embarrassment, and preferring to seek help from family or friends (Hinchliff and Gott, 2011). We now look at what health professionals can do to facilitate communication in this area.

Key points

- Health professionals experience barriers to asking older patients about their sexual health and sexual wellbeing.
- Patients do not always disclose their sexual difficulty during consultations.
- Patients want their doctors to be proactive.

Guidance for health professionals to improve their sexual communication

Taking a sexual history is a useful way to collect information about a patient's sexual background and to assess their current levels of sexual activity, sexual function, and feelings about their sex lives. It offers an opportunity for two-way sharing of information, and acts as an indicator of where to go next. Althof, Rosen and colleagues (2013, p. 27) argue that taking a sexual history can 'strengthen the therapeutic alliance' because patients feel as though they are being understood and taken seriously. Further, a sexual history can provide baseline information that will be useful not only at the outset, but during future assessments as it can highlight issues that are causing sexual difficulties. This is important in the area of gerontology and psychiatry where multiple medications may be prescribed. Taking a sexual history at the initial visit and during routine consultations can allow the identification of problems caused by prescription drugs. Indeed, if a change in sexual function or response is noted within four weeks of introducing a new drug, then it is likely that the drug is to blame (Dean, 2015).

Researchers have found there is often reluctance among health professionals to take a sexual history, which is usually due to the perceived acceptability of the topic of sex at a social, institutional, or individual level (Virgolino et al., 2017). Other concerns include uncertainty about how to ask the questions, when to ask them, and where

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(Fitter, 2015). We therefore propose the 'Three Ps' approach to sexual communication with patients.

The 'Three Ps'

The 'Three Ps' approach provides practical advice on talking to patients about sex, including how to start the conversation, and ways to facilitate comfort for both the patient and clinician. The 'Three P's approach is based on a review of the literature,¹ and focuses on Privacy, Permission, and Practice.

Privacy—this entails two key aspects:

Ensure that the consultation takes place in a private setting to avoid being overheard or interrupted. Let the patient know that discussions are confidential (and that confidentiality will only be breached under certain circumstances in line with the policy of your service, usually when the patient or another person is at risk of serious harm).

Permission—which works in two ways:

It is imperative that the clinician lets the patient know that they can talk about sexual matters by giving the patient permission to raise it in the consultation. And that the clinician will be comfortable when it has been raised. Clear signs of discomfort (such as fidgeting with a pen, avoiding eye contact) can close down any conversation on this topic because of its sensitivity. To start the conversation, clinicians can request permission to ask about the patient's sex life. Generic questions are helpful here (discussed further on).

Practice—which includes ensuring patient comfort to help disclosure. There are various ways to do this:

Help the patient to feel more at ease by making the consultation less formal (e.g. not sitting directly behind a desk). Consider your own non-verbal behaviours: eye contact and active listening are important skills. Use diagrams, magazine articles, leaflets to help communicate about sexual matters. Develop a set of standard questions, or one opening question to help start the conversation.

Generic questions are useful to begin the conversation, and to ask for/give permission to talk about sex. There are many ways these questions can be phrased; we offer some suggestions here:

'People who I see in clinic sometimes have sexual problems. Have you noticed any difficulties?'

'Sexuality is an important part of life, so if it's okay with you I'd like to ask you some questions about sex as part of your health assessment.'

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'Just a few more questions, if that's okay. At this point I normally ask some questions about your sexual health.'

'As part of your assessment, I can take a sexual history. The questions may be sensitive, but they are important and can help me to provide the best care for you.'

'These medications are known to cause sexual difficulties for some people, is that something you have experienced?'

'Some patients lose interest in sex. Is this something that has affected you?'

'Women can experience sexual difficulties around the time of menopause. Have you been affected in this way?'

More direct questioning can follow. As mentioned, the preferred context to take a sexual history is during the patient's first full assessment, rather than when a difficulty has been highlighted. However, this may not be achievable in practice, so remember that taking a sexual history can be executed at any point in the patient's treatment pathway.

The format of a sexual history does not need to be prescriptive: it can be designed to fit the patient group and service provided. It can be tailored accordingly; however, Fitter (2015) suggests that the following areas should be included: the nature of the current sexual problem and the patient's understanding of it; past and current medications (including prescribed, non-prescribed, herbal, performance-enhancing); and past and present sexual relationships, including sexual orientation and gender identity. For specific items to include in these categories, see Fitter, 2015, p. 18.

Other considerations on sexual communication with patients include being aware that they may prefer to talk about sex with a doctor of the same sex and age group as themselves (Hinchliff and Gott, 2011; Omole et al., 2014). This might especially be the case when cultural or religious factors influence who a patient is able to talk about sex with. Taking a sexual history should always be carried out in a way that is culturally sensitive. Likewise, it is important not to assume that patients are heterosexual, particularly during initial consultations. The use of neutral terms such as 'sexual partner', rather than terms such as 'husband' or 'girlfriend', can help avoid this.

Given that the topic can be sensitive, clinicians should bear in mind that a longer appointment may need to be scheduled (Fitter, 2015). Also, that an appointment for the couple may be required. While potentially valuable in that the session provides a safe space to build trust and confidence in sharing information, risks include the patient feeling inhibited to share information in the presence of a partner (Fitter, 2015). Careful consideration of this issue is required. However, remember that referral to appropriate services may be the best course of action. Balon (2015)

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argues that sexual difficulties associated with psychiatric disorders are often complex and difficult to manage, and they may require specialist intervention.

Activities to develop staff skills

It is important that clinicians are aware of their own prejudice and should not make assumptions about a patient's sexuality, including whether or not the patient is sexually active, and the type(s) of sexual activity in which a patient engages (Balon, 2015; Taylor and Gosney, 2011). To improve our own awareness of sexuality and comfort in approaching the topic with patients, reflecting on our beliefs about sexuality and attitudes towards sex can be particularly useful. The following questions (adapted from Hallett and Rees, 2017) can guide the reflective activity:

1. Do you consider your patients' sexual health and wellbeing needs? If not, why not?
2. Do you find it difficult talking to patients about their sexual health and wellbeing? If so, why do you think that is?
3. Do you make assumptions about your patients' sexuality?
4. Do you feel comfortable with some people more than others? Why is this? It could relate to assumptions about people and stereotypes e.g. that people who are old, or with a disability, are not sexually active
5. Do you find yourself making judgments about the types of consensual sexual activity a patient has? For example, if they engage in non-traditional practices such as having more than one partner at the same time, group sex, or bondage, discipline, dominance/submission, sadism/masochism (BDSM). If so, why do you think that is?

Another useful activity to help develop communication skills in this area is to observe clinicians who work in psychosexual services (Fitter, 2015). Through training and clinical experience, they have acquired and tested techniques which put patients at ease when discussing sexual issues.

Conclusion

As noted earlier, it is recommended that sexuality is approached from a biopsychosocial model. Taking consideration of the biological, psychological, and social factors that can contribute to sexual difficulties can help us to fully understand and address them. The biopsychosocial model ensures that health professionals consider far more than the biomedical model allows, including the relational, interpersonal, and everyday contexts within which we live our lives. While approaches to treatment for sexual difficulties will vary depending on the specific problem(s) experienced, alongside the mental and/or physical health of the patient, there are some general, yet important, principles to consider. These include viewing the sexual difficulty in context of the patient's intimate relationship. Here, it is important to identify whether or not the

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sexual difficulty is a cause of distress, and whether distress is experienced by one or both partners. Relationships can be negatively affected by sexual difficulties, but relationships can also act as a significant source of support and buffer the negative impact of a sexual difficulty. To be a reflective practitioner we also need to be aware of the cultural determinants of the patient's sexuality, as ethnic background can influence what is considered to be a sexual difficulty and the approaches to treating it. Similarly, it is beneficial to identify beliefs that the patient may hold about sexual activity, and help them to negotiate around any unhelpful ideas and expectations.

To achieve the sexual rights of older people we must remember that in many countries older people are marginalized and subjected to damaging prejudice and discrimination simply based on their age. And when being old intersects with other social categories that are in the minority, such as sexual orientation, gender identity, and race, older people can be further marginalized. To add to the mix, individuals with a psychiatric diagnosis may have experienced a lifetime of prejudice and discrimination. It is thus imperative that clinicians are aware of the vulnerabilities that older patients can feel, that professional practice focuses on treating older patients with dignity and respect, and that services ensure that a sexual rights framework is in place.

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Notes:

1 In particular, the work of Althof et al., 2013; Fitter, 2015; Omole et al., 2014; and Taylor and Gosney, 2011.



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Ethics and old age psychiatry

Chapter: Ethics and old age psychiatry

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Introduction

Ethics is about right and wrong, good or bad. Our decisions, if ethical, reflect our morality. It is reasonable to ask what the difference is between ethics and morals. The answer is that the words are mostly used interchangeably. But we can say this:

At root there is not much difference between the two words. 'Ethics' comes from Greek and 'morals' from Latin. Some people use the words slightly differently while others use them interchangeably. Many people associate 'morals' with deep-seated inclinations and intuitions. 'Ethics' are sometimes taken to be the rules and regulations of a group. [...] Ethics can be taken to imply the science of moral reasoning, while moral philosophy can be taken to imply the study of ethical debate and discourse. In

essence, both words are concerned with discriminating good from bad, right from wrong (Hughes and Common, 2015).

A simple way to consider matters would be to say that we have ethical standards as professionals that govern what it is to be a good doctor, nurse, or social worker, and so on, but we have deeper-seated moral obligations as human beings. This is simplistic, because it makes it sound as if somehow professional ethics is a less important topic. It is true that, just as we might sometimes break the law, so too we might ignore professional ethical standards. But there are two points: i) this would be exceptional; and ii) we would have to face the consequences. By and large, our professional ethical standards reflect our deeper-seated moral inclinations. If they did not, then on the grounds of conscience we might (exceptionally) consider breaking them. In any case, what we consider in this chapter are the underlying moral or ethical bases upon which we make our judgments and decisions.

The first point we are going to make is that all clinical decisions are, at one and the same time, ethical by nature. The same idea is conveyed by the idea of values-based practice (VBP), which I describe. We then go on to consider the major ethical theories and approaches. But at this point I raise a question about how we actually put ethics into practice. In the hurly-burly of clinical practice, it seems idealistic to think that we apply moral theories to the decisions and dilemmas we face in a calmly rational and logical manner. I suggest that the notion of patterns of practice might be a useful way to think about what we actually do. I explore this more fully in due course. In clinical practice, we face a huge array of ethical issues, especially in connection with dementia, but in other areas of old age psychiatry too. I highlight such issues, but I also demonstrate that the notion of patterns of practice is useful when we are thinking about these issues.

Clinical decisions are ethical decisions

The most everyday clinical decision, to discharge someone from follow-up, for instance, might be fraught with ethical dilemmas. Have I discharged him too soon? Am I just responding to managerial pressures not to keep people on my books too long? Have I discussed it with the patient in a suitable manner? Was he properly prepared? Are there enough support mechanisms in place? Should I have spoken with his daughter before discharging him? Does he really understand how to take his tablets? Will they be properly monitored by the general practitioner (GP)? Could he still be suicidal? These are all questions and worries about whether I did the right thing. The point to note is that they are also questions and worries about whether I have been a *good* doctor. To take another example, old age psychiatrists should know when and when not to prescribe an antipsychotic, and they should know the correct dosages to use. In all such cases—and this is the point—at one and the same time,

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as well as doing things in a ‘technically’ correct manner, being a good old age psychiatrist entails knowing and doing the right thing ethically.

If I have not properly prepared the person for discharge from follow-up, if I give the antipsychotic solely to settle the complaints from the care workers without thinking about alternative approaches, it is not just that I’ve performed poorly in a technical manner, it’s that I’ve failed to be a *good* clinician. Even if all I do is get the dose of a drug slightly wrong, there is still an ethical component to it. Whatever the excuses, which may be very reasonable (perhaps I’m overworked), I *ought* to get the dosages right. The ‘ought’ is a moral ought. It says that, potentially, I’ve failed in some sense as a good human being if I get this wrong. Getting the dose wrong is not a *good* thing to do. It may not mean that I’m a *bad* human being, but I still have not been as good as I *ought* to be, even if there are plausible excuses and even if the drug error is inconsequential.

I think there are several important points to be drawn from this. To be *good* doctors or nurses or occupational therapists or whatever, by definition we must be professionals who act ethically. Now in many cases, most in fact, the ethical dimensions of our practice will not be overt. I might prescribe paracetamol for a headache knowing instinctively that this is all that is going on and that nothing else needs to be considered. No ethicist is required: it is an easy clinical decision. But this does not mean that such a decision has no ethical connotations. All such decisions are made in the context of an ethical or moral field. After all, I could ignore a complaint about a headache. That I pay some attention to it is driven by my standing as a doctor, where the good thing to do, *qua* doctor, is to take account of the patient’s symptoms and signs. My decisions and judgments are in a sense determined by the background or context, which informs or shapes them, which makes them the clinical or professional judgments that they are (Hughes and Ramplin, 2012).

There will be times when the decisions are more overtly ethical, when I and the team struggle to decide what is right. Perhaps the decisions are so difficult that we need outside advice from a more experienced clinician, who will—just by dint of being more experienced clinically (according to the analysis I’m offering)—also be more experienced at making difficult ethical decisions, whether or not this is recognized. Or, occasionally perhaps, we shall need advice from a clinical ethics committee, where the combined expertise of several different types of professionals and of ethicists can come to bear on a difficult ethical dilemma.

Another point to be drawn from the statement that clinical decisions are ethical decisions concerns the status of the ‘technical’ aspects of the decisions that we make in old age psychiatry. They carry, inherently, ethical weight. That this patient now satisfies the criteria to be given electroconvulsive therapy (ECT) is not *merely* a technical decision. In itself it is (or is not) the ethically right thing to consider: in making this technical decision we are aiming at doing good. But the technical aspects

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of our decisions are not the whole deal. This is precisely because they are made in the context of an ethical field. Mostly the technical and the ethical will go together without our even noticing it. Even if we have made a completely correct technical decision, however, it does not follow that the decision is the right one. Perhaps ECT is indicated, but the patient wishes to wait a little longer and the dangers in waiting can be managed by careful nursing. But what if the dangers are too great? It is yet true that this technically correct decision still needs to be made (and then enacted) in the ethically correct manner. The rightness or wrongness of the decision is not decided purely on technical grounds. Who, for instance, has been involved in the decision? Has the patient been consulted and in what way? Should the decision involve the family? Hence, whether or not the clinical decision is a good one is decided not by the technical but by the ethical details of the case. Indeed, we might decide to do something that 'technically' does not seem best, but might nonetheless be the right thing ethically and we should do it for this very reason. Despite the evidence of psychosis, for example, we agree not to start treatment this week, even if technically we could use compulsory powers to do so, because we wish to establish a degree of trust and a therapeutic relationship with the patient by showing that we respect his views. The ethical trumps the technical because this *is* good clinical practice: clinical decisions are ethical decisions.

Ethics informed or shaped the practice of old age psychiatry when it was in its infancy and it will continue to do so, however technically advanced the field becomes. This is not to downplay the importance of technical know-how, because any professional ethic worth its salt should require that its practitioners are technically competent and up to date.

Yet, *how* we do things will often be of more importance than exactly *what* we do. In this vein, writing of virtue ethics as an approach (to which we shall return shortly), Hursthouse says:

Although I am, personally, sympathetic to doctors rather than otherwise, one does hear occasional hair-raising stories about the arrogance and callousness of some. What people often complain about is not whatever decision the doctors made, but the manner in which they delivered it or acted on it (1999, p. 48)

Values-based practice

Before turning to consider ethical theories and other approaches to ethical issues, it seems worthwhile to notice that the idea that all clinical decisions are at one and the same time ethical is mirrored in VBP, which is regarded as complementary to evidence-based practice (EBP). The evidence and facts are always going to be important, but we must not forget the values. Part of the benefit of VBP is that it reminds us that values are ubiquitous: they are never absent and must always be attended to if things are not to go wrong. Our values guide our actions, but so too

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does evidence: they go hand in hand. Both must be understood. Consider, for instance, someone with severe panic disorder. It might be tempting to suggest a mixture of psychotherapy and medication. But, of course, if the person's values were such that she hates medicines (say she believes in homeopathy) there would be little point in offering medication. A person, on the other hand, whose values were on the side of biomedical interventions, who could not see the point of waiting for talking therapies to work, would not be a candidate for psychotherapy. In both cases, the same evidence base might apply, but it is the values which make the difference in terms of what will work.

VBP describes a process of ten elements under four broad headings (see Table 51.1). It is 'a process that supports balanced decision-making within a framework of shared values where complex and conflicting values are in play' (Fulford et al., 2012, p. 24).

Table 51.1 The ten elements of the process of values-based practice (VBP).		
Clinical skills	1. Awareness of values	Being aware of the values that are in play is crucial to VBP, but it is a skill that must be acquired, especially when there are differences in values
	2. Reasoning about values	Having become aware of values, practitioners need to know how to reason about them, how to compare different moral stances, and understand them
	3. Knowledge of values	Awareness of relevant literature will support clinical decisions and allow negotiations around values
	4. Communication skills	Understanding diverse values and navigating between them will always require good communication skills
Professional relationships	5. Person-centred practice	The person, with his or her values, is always at the centre of the process

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	6. Multidisciplinary team work	But the input of an extended team is crucial, to include everyone concerned in a particular case since all views must be heard
EBP and VBP	7. The two-feet principle	Evidence is important, but so too are values: one cannot be used without the other
	8. The squeaky wheel principle	Values become most obvious when they are diverse and conflicting
	9. The science-driven principle	As science progresses the likelihood of values diversity increases, but both facts and values remain important
Partnership	10. Consensus and dissensus	If consensus can be reached, good; but when it cannot and there is dissensus it still remains important that all of the values, even the divergent ones, are acknowledged and remain potentially in play

Source: data from Fulford, K.W.M. (2004). Facts/values. Ten principles of values-based medicine. In: Radden, J. (ed.) The philosophy of psychiatry: a companion. Oxford, Oxford University Press; data from Fulford, K.W.M. (Bill), Peile, E. and Carroll, H. (2012). Essential values-based practice: clinical stories linking science with people. Cambridge University Press, Cambridge; data from General Medical Council (2017). Confidentiality: patients' fitness to drive and reporting concerns to the DVLA or DVA. GMC, London.

As well as recognizing values and their importance, VBP also indicates a process that can allow a situation to move forwards when there are difficulties. Imagine someone with advanced dementia where a decision has to be made about whether or not to pursue a treatment, such as antibiotics for a chest infection. It may be that there are different opinions within the care team but also within the family. It is important to acknowledge that there are differences first of all and to understand where they come from. Perhaps one daughter is placing heavy emphasis on something she heard her mother (the person with dementia) once say. Perhaps some staff are recalling how well a previous patient did when

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they received intravenous (IV) antibiotics in hospital. Perhaps it is a son who has deeply held religious beliefs that motivate his desire for everything that can be done to be done for his mother. Good communication will allow the different values to be expressed and negotiated, so that it is clear what everyone is saying. Knowledge about some of the values, e.g. religious beliefs, might be helpful. Keeping the mother centre stage, along with her values, is important, but the values of others should not be ignored. It will be useful to have the input of all the members of the multidisciplinary team, so that different perspectives are represented. Although there are diverse values, it may be that a consensus can be reached once everyone's views have been aired. But it may be that, while acknowledging one person's unhappiness at the decision, e.g. not to instigate IV antibiotics in hospital, it is agreed that the situation will be reviewed daily and if things do not go as expected, then the decision can be changed.

Ethical theories

In this section I outline the main ways in which philosophers have understood ethics and ethical reasoning. Consequentialism, deontology, principlism, and virtue ethics are the theories that I outline here (see also Hughes and Baldwin, 2006). There are all sorts of other approaches to ethical thinking, summarized in Box 51.1, which are not all discussed, but the references provide further details.

Box 51.1 Theories and approaches to ethical issues

Absolutism

The view that certain actions are *always* wrong or *always* obligatory, whatever their consequences.

Care ethics

This can be seen as a development from feminist ethics, where care itself and the nature of care are regarded as the crucial components in deciding whether something is right or wrong.

Casuistry

Arguing case by case, in the light of basic moral instincts, but with regard to the important differences between cases.

Communicative ethics

The correct answer to an ethical dilemma requires a commitment to free and open communication on the part of individuals and institutions.

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Communitarianism

A tendency, over liberalism, to stress tradition, the community, and the social context of practices and of selves.

Consequentialism

The rightness or wrongness of an action depends on its consequences.

Deontological ethics

Certain actions must be done as a duty (*deon*) regardless (to *some* extent) of their consequences.

Emotive theory

Moral language is intended to convey and to elicit an emotional response; so, an ethical decision mostly reflects an emotional, rather than a rational, response.

Feminist ethics

Taking into account experiences and values more typical of women than of men, feminist ethics stresses the importance of interdependent relationships in which caring for others is implicit in a person's moral life.

Hermeneutic ethics

Actions should be judged by an interpretation that allows their meaning in a context to be understood.

Intuitionism

What is right can be directly seen (or intuited) by the mind or conscience.

Liberalism

The guiding light of western democratic traditions, which stresses the need to respect each citizen as free and equal; as such, associated with the notion of *egalitarianism*, which stresses the primacy of equality.

Narrative ethics

The rightness (or wrongness) of an action will become apparent in the context of a detailed story.

Natural Law ethics

A moral theory favoured by the Catholic religious tradition: reason can determine basic human goods, constitutive of human flourishing, which ought to guide action.

Perspectivism

The way to seek the right thing to do is to take account of the different perspectives on any given situation, which will make it more likely that answers to problems have greater validity. This approach to philosophical problems is associated with the name of Friedrich Nietzsche (1844–1900).

Prescriptivism

Moral terms are used primarily to guide action, to tell people what to do.

Principlism

Beneficence: doing good;

Nonmaleficence: avoiding harm;

Autonomy: allowing self-rule;

Justice: distributing goods fairly.

Prioritarianism and sufficientism

These are approaches used in connection with resource allocation. 'Prioritarianism is the view that we ought to give priority to benefiting those who are worse off. Sufficientism, on the other hand, is the view that we ought to give priority to benefiting those who are not sufficiently well off' (Brown, 2005).

Religious ethics

What is right or wrong depends upon religious traditions (e.g. *Halakah* in the Jewish tradition; *Sharia* in the Islamic tradition) or precepts.

Situation ethics

In ethical dilemmas in medicine, issues must be decided on the basis of the actual situation: different decisions reflect different situations.

Utilitarianism

A form of consequentialism that takes the maximization of pleasure (and the minimization of pain) as the measure of a good action.

Values-based practice

Involves acquiring practice skills that encourage practitioners to look carefully for the values (as well as the facts) at play in clinical practice and to seek ways to be as inclusive as possible in negotiating outcomes in the light of mutually recognized but sometimes diverse values.

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Virtue ethics

What counts in ethics is the habitual disposition of the person: an action is good if it reflects a virtuous character.

Notes: For further details and theories the reader should consult the sources of this table: Honderich (1995) and Ashcroft et al. (2007). Communicative ethics is discussed in Moody (1992). For hermeneutic ethics see Widdershoven and Berghmans (2006). For more details about values-based practice, see Fulford (2004). Amended from Table 36.1 in Hughes, 2002.

Adapted with permission from Hughes, J.C. Ethics and the psychiatry of old age. In: Jacoby, R. and Oppenheimer, C. (Eds) *Psychiatry in the elderly*, 3e. Oxford University Press, Oxford, UK. Copyright © 2002, OUP.

There are, however, two general points to be made. First, it is interesting that a number of the approaches in Box 51.1 are similar in that they stress context and relationships. Care ethics, communicative, hermeneutic, and narrative ethics, for instance, all place some emphasis on the concrete circumstances of real individuals who need to be understood in particular times and places. This is one of the things that make these approaches to ethical problems and thinking so appealing: they embrace the real-life messiness of moral decision-making. But this focus on the particularities tends to go against the idea that definitive statements can be made in advance of actual situations. There are deep issues lurking here, which cannot detain us for long, but which it seems important to acknowledge.

When doctors (and others) find themselves discussing ethical issues, one of the most commonly heard statements, at least in my experience, is that there are no right or wrong answers in ethics. I fully appreciate why people make this statement. One reason is precisely because the particular circumstances of each individual case will be what make the difference. Recall that it is the focus on the real particulars that makes these approaches appealing, in that they are not just theoretical and abstract, but engage with the clinical realities. These realities are as various as the cases from which they are drawn. In one, it might be the serum potassium that helps to decide the right thing to do; in another, it might be the fact that the patient's daughter lives abroad that determines the action that is taken. In most cases, it will be an amalgam of biological, psychological, social, legal, familial, cultural, and spiritual factors, and so on, that will lead to a particular course of action being chosen. In many cases, from the ethical perspective, it might be reasonable to do either A or B. For instance, it might be ethically reasonable, in the case of the person with a severe depression, either to wait a further week to see if the antidepressant is starting to work or to go ahead this week and give ECT. This is not, however, the same as saying there are, ethically, no right or wrong answers. It certainly would not be acceptable in the case I am

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imagining to do *C* or *D*, where these involve either stopping all treatments and discharging the patient or beating him twice a day with the leaves of the plant celandine. In other words, there *are* right and wrong answers.

Sometimes there is more than one right answer; and sometimes we cannot be sure what the right answer is. But the point of ethical debate is to move towards the good outcome, to try to do or to clarify the thing that is right; and if this were not the case, there would be no point in the debate in the first place. In saying this, I am taking a stance against a type of subjectivism in morals: I do not think that morality simply boils down to matters of taste. But, of course, not all philosophers have agreed with this (see Mackie, 1977). Nevertheless, I claim that there is some horizon, which can be argued for on rational grounds, against which our arguments and actions must be judged (Taylor, 1991). There are right or wrong answers in ethics, just as there are in clinical practice.

The second point I draw from Box 51.1 follows from the earlier discussion. For if there is such a variety of theories and approaches, how can we know which to use in any given circumstance? One approach might give us one answer and an alternative might give us some other answer. Is there a rational way to pick between them? Is the point that we should decide on which approach or theory is the best and then always stick to that one? Or can we pick and choose? In which case, is there a rational way to do this?

I think the answers to these questions are important. They may, in a sense, be disappointing answers. Doctors and other healthcare professionals are, by nature, practical people. We are typically faced with problems (e.g. of diagnosis or treatment) for which we wish to have solutions. One appeal of clinical ethics is that it can help us by offering solutions to the practical dilemmas we face. To some extent I think it is true that clinical ethics achieves this. If we are faced with a difficult treatment decision, then of course the right thing to do will be to discuss it with the patient. It is easy enough to give reasons why we should do this, for instance, to respect the person's autonomy. If the person is unconscious or incapable, we may still be able to find ethically justifiable ways to respect what would have been his or her autonomous wishes by looking for advance directives or by seeking the views of relatives.

The disappointing answer is that, notwithstanding the evident practicality of clinical ethics, perhaps it never was a realistic expectation that moral reasoning would provide practical solutions in any direct sort of way. To come to the point, the theories and approaches of Box 51.1 give us ways to think about difficulties, without necessarily giving us answers. In certain situations, it may be helpful to think in terms of narratives: this will help us to understand the lives of our patients with dementia, which will in turn make it more likely that we shall think in a manner that is appropriate if we are now having to make decisions about treatment at the end of life. If we think through a problem, keeping in mind the different perspectives of all concerned, as in perspectivism, we are more

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likely to make the right decision about the treatment for the recidivist drug abuser. Taking the communitarian approach may help us to reach better decisions about how to deal with problems associated with a particular nursing home, because we are more likely to take a broader view and consider the historical and social context for patients, relatives, and staff.

It is still, however, necessary to take a practical view of matters: these ethical approaches must help us to arrive at this or that solution. But there is something deeper, too, because moral theories also provide us with ways of understanding our moral inclinations, not just with answers to practical problems. In other words, when I decide that I should break confidence and report a patient whom I consider to be driving unsafely, it is not necessarily because I have been through a process of ethical reasoning. It may just be part of the clinical protocol. But having acted thus, or perhaps having decided that the psychotic patient needs to be detained under compulsion, I can use the various ethical theories to provide my actions and decisions with a rational basis. We can understand the ethical structure of the world through these theories in a similar way to how we understand the physical structure of the world through physics and chemistry. My knowledge of atoms and electrons does not affect the way in which I walk down the street. Even if they do not help me to argue, ethical theories give me an insight into the rational structure of thought and into the history of ideas so that my judgments stem from an informed background. This background may be of some practical help when I am faced with a dilemma, just as knowing about electrons may in some way be useful for the medical physicist. More than this, it could be argued that understanding the nature of ethical issues around the practice of medicine simply makes us receptive to the nuances of language, meaning, and emotion in our multi-layered encounters, which will in the end make us better practitioners. Whether or not this argument—about how moral reasoning may have practical implications but is also valuable in itself as a means of understanding the world—can be defended, it is not one that I shall pursue here. But I shall come back to the question of what it feels like to make ethical decisions and how it can feel almost automatic, as if there is no real ratiocination.

Consequentialism

Consequentialism is the idea that our actions are properly judged to be right or wrong on the basis of their consequences. The best-known form of consequentialism is utilitarianism. The classical Utilitarians, Jeremy Bentham (1748–1832) and his godson John Stuart Mill (1806–1873), regarded happiness or pleasure as the main outcomes to consider in terms of consequences; but, of course, there could be other consequences of actions, such as knowledge, success, and the nature of relationships, that could be used as ethical markers if we wished. Utilitarians might respond that these other factors are simply markers of different types of pleasure or happiness. Nevertheless, consequentialism and utilitarianism do not need to be regarded as the same thing and we might decide that

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the broader notion of consequentialism seems more useful in clinical ethics.

Perhaps a more significant distinction is that between act utilitarianism and rule utilitarianism. Act utilitarians consider particular actions and ask, in order to decide whether or not something is the right action, if it would maximize happiness or pleasure (and minimize pain). Rule utilitarians, on the other hand, look at whether or not acceptance of the rule, of which the act is an instantiation, would tend to maximize pleasure and so on. Thus, an act utilitarian might argue that we should say that people with mild dementia cannot drive because they might cause accidents. Although individuals with mild dementia will be upset and inconvenienced, happiness (or perhaps welfare) will be maximized by the avoidance of accidents. A rule utilitarian, alternatively, might be inclined to take a more sanguine view of people with mild dementia driving, on the grounds that to have a rule that they cannot drive would undermine broader conceptions of fairness in society and thereby reduce overall happiness (or welfare). The rule utilitarian can still accept that a particular person, Mrs Green, should be disqualified from driving if she fails some specific cognitive or practical test, which accurately predicts the likelihood of an accident, because to have a rule that involved ignoring accurate predictions of this nature would increase actual pain and decrease general pleasure in society.

So, even within utilitarianism, we can discover different approaches to similar ethical dilemmas. But the distinctions allow us to understand the ethical dimensions of our decisions more clearly. There are the consequences for Mrs Green and those with whom she might be involved—that is, both those she might help by retaining her ability to drive, and those she might harm by driving—and there are the broader consequences for society of making decisions in this one case that should then govern all.

Consequentialism is often compared to deontology, which concerns duties, to which I shortly turn. A typical example concerns lying. A consequentialist might argue that it is better to lie to a person with dementia because in this way you maximize happiness. So, it is all right to tell the person that his mother has said he can stay in the day-care unit, if this helps him to settle, even though his mother has been dead for some years. A deontologist might, alternatively, take the view that there is a duty to be truthful with people even if they have dementia, and so it should be explained carefully to the person that his mother has died and he needs to stay in the unit to be looked after properly; or, at least, that the lie should be avoided, e.g. by the subject being changed. In passing, it might be noted that in this case the deontological view might also be the view that the rule utilitarian would take; for to accept it as a rule that it was right to lie to people with dementia could conceivably be deeply undermining of social welfare. Again, we are presented with different ways of thinking about moral issues by considering different moral views.

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In the following sections, however, I discuss the possibility that each of the four main types of ethical theory would end up saying the same thing. Practically, therefore, there would be no difference between them in terms of outcome. But conceptually they are different, and by considering the same case with the same outcome we can see how the different theories allow us a different perspective on the world.

Case study 1 The Case of Miss Burns

Background

Miss Burns has always lived alone. She worked as a secretary in a local government office. She was known to be someone who could be relied upon to keep matters confidential. In retirement, she has enjoyed listening to classical music, but she has not tended to socialize. Her GP has received reports from neighbours, who state that Miss Burns is behaving in a gradually increasing paranoid manner, seeming to spy on them through her curtains and always avoiding social contact. When the GP visits, Miss Burns is reluctant to let her into the house, but when she does, the GP finds the house to be dangerously cluttered. It is very unhygienic, with evidence of infestations, and there is an obvious fire risk. The GP writes a referral to the old age psychiatry team. They find that, although Miss Burns is unwilling to be tested in a formal manner, a degree of cognitive impairment is evident. In addition, Miss Burns demonstrates some paranoid delusions. She will not accept any help, and all concerned decide that it would be reasonable to assess her further as an inpatient using compulsory powers to detain her. But they are aware that this will be very distressing for Miss Burns. Are they doing the right thing?

Comment

In discussing this case, we have to presume that the GP and the old age psychiatry team have thoroughly assessed the risks and genuinely explored options other than compulsory admission. The consequentialist would, I think, find little difficulty in giving an opinion on the case. Of course there may be some bad consequences following an admission: being removed from her house will be traumatic for Miss Burns; she may suffer side effects of any psychotropic medication she is given; she may decompensate once she is out of her own environment so that it becomes harder for her to return to independent living. But there are bad consequences to her staying in her home: she may become ill because things are so unhygienic; the infestations will shortly affect her neighbours; her paranoid behaviour is attracting the attention of the local youths who seem inclined to victimize her; she may inadvertently cause a fire. And the good consequences of assessment and treatment are also more than probable: she will be kept safe; her health will be

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maintained; she might settle into a new environment where she can be cared for and where she might be happy; or she might return to live at home more comfortably with appropriate support. In addition, her neighbours will not be put at risk by her behaviour. Similarly, a rule utilitarian would have little difficulty in concluding that a rule which stated that people who were putting themselves or others at risk and were not willing to accept help should, to maximize happiness, be subject to compulsory treatment. In the view I have presented, therefore, a consequentialist appraisal of the case of Miss Burns would support the use of compulsory powers, at least to assess her.

Deontology

The deontologist is someone who believes that there are things one *must* do (the Greek verb *dei* translates as 'ought', describing a 'necessity' or a 'must'; *deon*, then, means 'duty' and *logos* translates as 'reason'). In other words, ethics is to do with duties and 'deontology' suggests reasoning based on a sense of duty. If utilitarianism is associated with the names of Bentham and Mill, deontology is often associated with that of Immanuel Kant (1724–1804). He argued that the rightness or wrongness of an action cannot depend on its consequences. More important, in his view, is the motive or the will of the person performing the action. A person might do something for good motives and yet it might have bad consequences or, contrariwise, the person may be willing something bad, but nevertheless the consequences of the action are good. Someone who is well motivated will respect the moral law, according to Kant, which will involve acting from a sense of duty, that is, on the basis of what must, of necessity, be done.

If we were to look more closely at the philosophy of Kant, we might be struck by a similarity between his notion of a categorical imperative, which provides the underpinning motivational grounds for our actions when they are right, and rule utilitarianism. One way in which Kant formulates the categorical imperative is to say that we should only live by maxims that could be made into general laws. Ignoring the intricacies of Kantianism, however, it is easy to see how the deontologist might well also agree that Miss Burns should be compulsorily detained for further assessment and perhaps treatment. We would not wish there to be a universal rule that people who were failing to look after themselves and were thereby becoming ill and threatening the health of others should be left to their own devices. We might well argue that a civilized society ought to be caring for those who are ill and unable adequately to care for themselves. We might also, more simply, state that we have a duty to care for people like Miss Burns. The argument is not based on the good or bad consequences of what we might have to do; it is more directly that the moral law tells us where our duties lie. The Golden Rule, 'Do as you

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would be done by', which is found in almost all religions, is another way of expressing Kant's notion of the categorical imperative. It is then reasonable (i.e. rational) to say, if we were ill in the way that Miss Burns appears to be, we would want people to help us, even if we could not appreciate the need for such help. The key thing, however, is that the action is motivated by good will informed by universalizable reasons. The goodness or badness of the action does not depend on its consequences.

Principlism

The so-called four principles of medical ethics (see Box 51.1) have been set out over a number of years by Tom Beauchamp and James Childress in their book *Principles of Biomedical Ethics*, which is now in its seventh edition (Beauchamp and Childress, 2013). The book is about much else besides, but the four principles have become a way of summarizing in a useful manner much thought in the field of bioethics (Gillon, 1986). As Gillon (1994) said about the four principles approach: 'It offers a common, basic moral analytical framework and a common, basic moral language'.

We can, thus, use the four principles—autonomy, beneficence, nonmaleficence, and justice—to discuss the case of Miss Burns. Respecting autonomy is the thing that makes us put off intervening too soon. We know that, under normal circumstances, Miss Burns has the right to determine her own future, to make choices about how she lives, and to decide for herself when she wishes to seek help. The difficulty is that there must be limits to autonomy, even though it is often regarded as the primary principle. Normally, to guard against paternalism (i.e. doctors, or anyone else, thinking they know what's best for someone), stress is put on the idea that the individual is best placed to decide for him- or herself what should happen. But this principle cannot ride roughshod with no concern for the rights of others. The etymology of 'autonomy' suggests the notion of self-rule. For any individual, the area over which I can exert my rule will be limited, not only by others who also wish to rule their domains (so that our areas of dominion come up against those of others), but also by biological, psychological, social, or alternative circumstances, which mean that I cannot exercise self-rule apart from in a circumscribed fashion. Under the current arrangements (i.e. with no help or support and given the nature of the threats she poses to others), Miss Burns cannot continue to live independently without at least some investigation, if not some treatment.

The principle of beneficence comes into play under the current circumstances. All those concerned wish to do Miss Burns some good. The principle of beneficence suggests that we must aim to help her. At the same time, we must do this without causing her any harm, or at least we must limit the harm that we do insofar as this is possible. This is in keeping with the principle of nonmaleficence.

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Finally, there is the principle of justice, which entails that we should deal with people fairly. In the case of Miss Burns, this principle might be used to support the use of compulsory powers. Such powers ought always to be used in a fair and equal manner. In addition, justice demands that people should have rights of appeal against decisions to remove their liberty by compulsion. The principle of justice is also used in connection with resource allocation. A case might be made that not to detain Miss Burns would lead to increasing costs in attempts to maintain her in as good a state as possible in the community. But such *costs*, particularly in the face of her refusal to comply with the measures that would have to be established, might be prohibitive; and in addition, when weighed in the balance, the *benefits* of ameliorating matters by admitting her for further assessment seem more than likely to outweigh trying (probably unsuccessfully) to look after her at home.

Virtue ethics

The four principles give us an easy-to-recall 'moral language' (Gillon, 1994). In a sense, virtue ethics changes the language altogether. In so doing it also extends it. If, very roughly speaking, consequentialism looks at outputs ('do it because it leads to X') and both deontology and principlism look at process ('do it because it is in accordance with Y'), then virtue ethics tells us to look at the input ('do it because it comes from Z'). The virtues are inner dispositions, such as honesty and compassion. Virtue ethics says that you should do what the virtuous person would do. (For the best detailed philosophical account of virtue ethics, see Hursthouse, 1999.) We might object that the judgment that someone is virtuous seems highly subjective (what if I said that I thought Hitler was a man of virtue?!). Virtue theory, however, has an inbuilt defence against this objection, because a virtue can be defined in terms of human flourishing. If we had to characterize what it is to be a good human being—what it is to flourish humanly, that which is admirable in the human character—we would quickly find ourselves using the virtue words. In this sense, virtue ethics extends moral language far beyond the four principles.

Objectivity comes from the background agreement that the good person is the one who demonstrates compassion, integrity, honesty, and so forth. Even when we know their shortcomings, there are people in the world whose virtue is readily recognized: Mother Teresa (1910–1997) was one and Nelson Mandela (1918–2013) another. But we do not have to look to the world stage to find examples of virtuous people. There will be people around us, friends or colleagues to whom we turn for advice precisely because we recognize their virtues. We go to them, and not to some others, because we know them to be honest, to have integrity, and to be people of practical wisdom. We go to them because of these virtues.

One criticism of virtue ethics has been that, while providing a good description of human character, it does not actually direct action: it does

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not tell us what to do. Again, however, virtue ethicists have a direct response this:

Not only does each virtue generate a prescription—do what is honest, charitable, generous—but each vice a prohibition—do not do what is dishonest, uncharitable, mean (Hursthouse, 1999, p. 36)

Virtue ethics has had a renaissance in recent years, including in connection with medical practice (Pellegrino and Thomasma, 1993). It is usually taken to derive from Aristotle (384–322 BCE). From Aristotle, for instance, comes the notion of ‘human flourishing’, which is a frequent translation of his term *eudaimonia* (ευδαιμονία). A useful brief account of virtue ethics is provided by Oakley (2007). But there are reasons to think that we—as professionals—should pay this ethical theory more attention.

The concept of a virtuous character has been portrayed as central to professionalism [...] Traits such as trustworthiness, fidelity, honesty, and integrity have been identified with professional status (Radden and Sadler, 2010, p. 69).

To return to the case of Miss Burns, the virtuous professional, because of his or her compassion, practical wisdom, honesty, fidelity, and courage, will take the necessary steps to make certain that Miss Burns is well looked after and cared for appropriately. This will involve, up to some point, supporting her in the community; but when the time comes, the right thing to do will be to use compulsory powers to detain her for assessment and for treatment as required. To fail to take this step would be a failure in terms of compassion, practical wisdom, honesty, and the like. The professional would not be a good professional, would not flourish as a doctor or social worker, for instance, if he or she were unwilling to demonstrate the courage and the compassion occasionally required to take away a person’s liberty.

Elsewhere, I have argued that the virtues might also be used to support occasionally going against even authoritative guidelines—I was thinking of the guidelines established in England and Wales by the National Institute for Health and Clinical Excellence (NICE) governing the use of antimentia drugs (NICE, 2006)—on the grounds that not to do so would be to ignore the virtues that underpin social justice and human community (Hughes, 2012). More broadly, Radden and Sadler (2010) have argued that virtue ethics provides the most appropriate approach to moral thinking in connection with psychiatric practice. In order to show the richness of this approach, I have listed in Box 51.2 (and explained where this seemed necessary) the virtues (or the virtue-type words) highlighted by Radden and Sadler as relevant to psychiatry. To these I have added the virtues described by Pellegrino and Thomasma (1993).

Box 51.2 Examples of virtues for psychiatrists

Authenticity, sincerity, and wholeheartedness

These suggest the idea of being true to oneself.

Emotional intelligence

Empathy and compassion

Fortitude, patience, and perseverance

Gender-sensitive virtues

By this is meant the virtues of respectfulness of the patient's autonomy, tolerance, humility, self-knowledge, imagination, trustworthiness, scrupulosity, self-control, and gender sensitivity and awareness.

Genuine warmth

Hopefulness

Humble propriety

This suggests not just a pretence, but a genuine awareness of and sensitivity to the effects of one's words, behaviour, and deportment.

Integrity

Justice

This is not simply an attention to fairness with respect to resource allocation; as a virtue, it suggests a fundamental ability to make good judgements.

Moral integrity and leadership

Practical wisdom

This virtue is also seen as fundamental, for it allows deliberation about the ends or goals of practice and treatment, and the discernment to pursue the right path towards those ends or goals. It is sometimes called prudence or, to use the Greek word, phronesis (φρόνησις).

Realism

This term suggests that thoughts, beliefs, and responses are kept in line with the facts, to give a balanced appraisal and steady perspective.

Respect for personhood

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Self-effacement

In other words, a type of humility.

Self-knowledge

Self-unity

It is seen as useful for the therapeutic relationship if the practitioner has a unified and insightful sense of self.

Temperance

Usually this implies keeping check of one's appetites, but more broadly it can also be regarded as a form of self-mastery, which enables the practitioner to live an intelligent life, i.e. one in keeping with broader notions of human flourishing.

Trustworthiness or trust

Also conveyed by words such as 'fidelity', which suggests the idea of 'being true', and reliability.

Unselfing

This term refers 'to the personally effaced yet acutely attentive and affectively attuned attitude toward the patient, the relationship, and its boundaries, adopted by the ethical and effective practitioner' (Radden and Sadler, 2010, p. 132). This is not intended to be simply detachment, which involves an emotional distancing, since the doctor needs to be aware of his or her emotions and to use them appropriately.

Source data from: Pellegrino, E.D. and Thomasma, D.C. (1993). The virtues in medical practice. Oxford University Press, Oxford and New York; Radden, J. and Sadler, J.Z. (2010). The virtuous psychiatrist: character ethics in psychiatric practice. Oxford University Press, Oxford and New York.

The listed virtues do not follow the exact ordering of Radden and Sadler, Pellegrino and Thomasma, and the descriptions are not necessarily those that would be given by them. But Box 51.2 is enough to suggest that virtue ethics significantly broadens the view of what might be relevant in our ethical deliberations.

Summary

Let us make the assumption that we would all agree that Miss Burns requires compulsory hospital admission for assessment and perhaps for treatment. Albeit there might yet be some disagreement in real life if we actually brought together ethicists from these different theoretical

perspectives, we can see that the four ethical theories we have outlined each provide useful views. Of course, it makes sense to be aware of the *consequences* of our actions; these might well alter what we think it is right to do. But, at the same time, there is a *duty to care* for Miss Burns, whatever the outcome; and this duty to care is supported by the principle of *beneficence* and guided by the principle of *nonmaleficence*. We must respect her *autonomy*—the *rule utilitarian* would agree with this—but *justice* dictates that we have to think of the others involved, for example her neighbours, who might wish to argue on *act utilitarian* grounds that assessment and treatment are now required to maximize the welfare of all concerned. All of this, however, is motivated in the first place by those dispositions of character, the *virtues*, that come together to support broader conceptions about what it is to flourish in the world as human beings. Our concern about the outcome for Miss Burns, if it is ethical, is fuelled by our *compassion*; meanwhile, our discernment concerning the best outcome reflects *practical wisdom*, which we have acquired through training and experience; and our judgments about how to achieve the outcome are guided by an underlying sense of *justice*. Combining these ethical theories, therefore, gives us a rich and layered appreciation of the nature of the world of morals and values in which we live. Ethical theories give us perspectives on the world as surely as theories in physics and chemistry do. They also help us to live in and act on the world. But how we use our theories is not always as clear-cut as those theories sometimes suggest. The old utilitarian view that we could simply apply a felicific calculus (i.e. a machine-like calculation of happiness) to arrive at the maximum amount of happiness in order to guide our actions is about as primitive as the view that the earth is flat. How we put theory into practice in the real world is the subject of the next section.

Patterns of practice

In this section I suggest that the notion of patterns of practice¹ might provide a useful way to think about ethical decision-making. An immediate point to note is that, if this is so, patterns of practice might be useful not only in the clinical field, but wherever ethical decisions have to be made: in political life or in the financial world, for example. It is also only honest to acknowledge that this aim should, in large measure, be fairly easily achieved. Our ethical decision-making, whether in clinical, financial, or political settings, will sit within some pattern of practice or other. At least, most ethical decisions will be describable in terms of a pattern of practice. Only highly idiosyncratic or aberrant decisions are likely not to conform to some pattern or other; and, even then, their idiosyncratic or aberrant nature is likely to reflect the precise fact that they stand outside normal patterns of practice. So, of course patterns of practice—as a notion—can provide a way to think about ethical decision-making! My aim, however, is easily achieved only *in large measure*. The more interesting point is *the extent to which* the notion of pattern of practice is *useful*. My suggestion is that it is useful at the level of practice

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and at a profound philosophical level. Indeed, it is a notion that brings these levels together.

What are patterns of practice?

Patterns of practice are quotidian and pervasive. At a superficial level, we can hardly escape the extent to which our lives are patterned. Our routine behaviours, eating and sleeping say, tend to conform to patterns and we suffer when the behaviours are too radically disturbed. Social behaviour is also deeply reliant upon patterns of practice: safe driving, for instance. Even good manners are a matter of accepting certain patterns of practice and it is disconcerting when such codes of practice are ignored. Cultural patterns of practice can be observed in sporting arenas around the world, or in concert halls, with subtle and not so subtle differences depending on the precise type of sport or brand of music.

At a deeper level, perhaps, in the case of religions we speak of patterns of prayer or worship. There is an obvious philosophical debate to be had concerning whether such patterns merely reflect different sociocultural traditions, or whether the practices themselves are in some deeper sense constitutive of religious belief. To be of a particular religion is to engage in (and with) its patterns of worship. To fail to attend Mass on Sundays is to be a lapsed Catholic. Like other religions, Islam dictates certain practices: 'Recite from the Koran as many verses as you are able ... Attend to your prayers, render the alms levy ... Implore God to forgive you ...' (Dawood, 1956, p. 410). To disregard the precepts of any religion wilfully and persistently would be incompatible with the practice of the religion.

Something very similar can be said about clinical practice. Medical practice is full of patterned responses. We learn to take and report a history in a standard way. Particular routines for the examination of a patient are pursued. Particular symptoms and signs trigger certain investigations. One set of complaints triggers immediate admission to hospital; different complaints might prompt a referral to social services. Although there may be regional variations and occasional innovations in precise practice, if the pattern of practice is woefully wrong the doctor risks losing his or her licence to practise. Clinical patterns of practice also pervade how we communicate with patients and carers, how we think of them (e.g. as cases or as people), and ultimately how we treat them.

So far in this section I have: (a) shown the extent to which our personal and social lives are patterned; (b) gestured at the possibility that patterns of practice might not just reflect our beliefs, but might play a constitutive role in them; and (c) indicated how clinical practice is also patterned in a pervasive and ubiquitous fashion. Before moving on to consider the extent to which the notion of patterns of practice might be useful, I pause to consider two particular ways in which the idea of practice proves profound: first, in the context of the philosophy of thought and language; secondly, in connection with virtue ethics. In both cases I draw on the

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work of philosophers that helps to underpin my suggestion about the extent of the usefulness of patterns of practice in medical ethics.

Patterned language

To say that language is patterned might be to make a purely linguistic point about the structure of language. The philosopher Ludwig Wittgenstein (1889–1951) claimed that ‘To understand a language means to be master of a technique’ (Wittgenstein 1953, §199). This might be taken simply at this linguistic level. But Wittgenstein’s interest was in philosophical issues to do with meaning. In this regard, in his famous discussion of rule-following, he pointed to the normative nature of our descriptions of mental states. In other words, when I say that I understand something it entails that certain things are or will be the case. Saying something is normative is to establish criteria of correctness. It means that certain things are constrained to be the case. The mental state seems to exert its normative constraints over things that are not yet in existence; for if the content of the mental state is to have meaning, certain things in the world must be or will be true. Mental states with content—that is, my true beliefs, thoughts, wishes, and so on—just like rules (which govern the future), are similar in that they exhibit this normativity.

A wish seems already to know what will or would satisfy it; a proposition, a thought, what makes it true—even when that thing is not there at all! Whence this *determining* of what is not yet there? This despotic demand? (Wittgenstein, 1953, §437).

The conclusion of Wittgenstein’s famous rule-following discussion ‘is that understanding cannot be further explained other than as an ability to enact a practice ...’ (Thornton 1998, p. 35). According to Wittgenstein:

... there is a way of grasping a rule which is *not* an *interpretation*, but which is exhibited in what we call ‘obeying the rule’ and ‘going against it’ in actual cases [...] And hence ‘obeying a rule’ is a practice (Wittgenstein, 1953, §§201-2).

In the course of presenting his interpretation of Wittgenstein, Thornton puts it thus:

When one comes to understand the meaning of a word, one acquires an ability to use it correctly which cannot be further explained. One simply masters a practice or technique [...] Understanding a meaning is a piece of ‘know-how’, a practical ability. One way of putting this is to say that meanings and rules are individuated by practices and that understanding a meaning or a rule is thus individuated by the practice over which one has mastery (Thornton, 1998, p. 90).

When Wittgenstein himself is talking about how he might justify following a rule in the way that he does, he says:

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If I have exhausted the justifications I have reached bedrock, and my spade is turned. Then I am inclined to say: 'This is simply what I do' (Wittgenstein, 1953, §217).

In this adumbrated account, we see that certain types of mental state (understanding, remembering, meaning, and the like), represented by linguistic practices, are rule-governed. Their rule-governed nature manifests an essential normativity (things seemingly couldn't be otherwise than they are), but what this boils down to is a matter of practice. There are, of course, alternative interpretations of normativity (cf. Thornton 1998), but on the one being considered here the normativity of mental states amounts, somewhat shockingly, to a mere practice: 'This is simply what I do'.

Those aspects of our life that seem so essential to our make up as human beings—our ability to think, understand, believe, hope, remember—turn out on this interpretation to be practices, things that we do in a particular way simply because we are thus! These patterns of practice reflect our standing as agents of this type in the world. This is simply how we act in the world. The important point is that we act normatively. As Luntley says:

... our thinking lies in the pattern of our actions, where actions are causal encounters with the world. The normativity of thought is the normativity of the pattern/structure of our causal encounters ... We say that the patterns of our causal encounters with the world are irreducibly normative ... Some of the patterns that physical things, like us, get into are normative patterns (Luntley, 1999, p. 345).

The argument I have been wishing to imply, therefore, is this: language and thought are essentially normative; normativity is a matter of practice; thus, at heart our lives as embodied agents are situated in a realm of practices (Hughes, 2011). Hence, the notion of patterns of practice makes a profound link with our standing as human beings of this sort (with minds and language) in the world. These patterns of practice involve (constitutively) normative constraints, the despotic demand that we live thus and so, because this is how we are. In other words, there is an essential link between our actions, what we do, and how we have to be as human beings in the world. Elsewhere Luntley has said: 'The moral world has its being in, it rests upon, what we do and how we act. It is in our actions and the way we treat one another that values come into being and are preserved in being' (Luntley, 1995, p. 218).

With this thought, I turn to a connection between patterns of practice and the virtues.

Patterns and virtues

The emphasis on action and practices might, at first blush, seem to sit uncomfortably with virtue ethics, where the emphasis is more on the agent than the action. While it is true that virtue ethics stresses what the

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person *becomes* by acting this way or that (rather than, say, the consequences of actions), it is also true that virtue ethics is concerned with actions themselves inasmuch as these are specified by the virtues. To the prescriptions and prohibitions of the virtues and vices, virtue ethics adds a corrective by focusing attention on how the action is performed. The right action, done badly, might be as harmful as the wrong decision.

Hursthouse (1999) argues that, even if virtue ethics can generate action guides (i.e. 'do this' or 'don't do that'), there are reasons to pull back and consider *the agent* in our judgments of moral action. For one thing, she argues, this allows room for regret, even if the right action has been performed. With explicit reference to medical practice (in the continuation of a quote we've seen earlier) she contends:

... if someone dies, or suffers, or undergoes frightful humiliation as a result of [a doctor's] decision, even supposing it is unquestionably correct, surely regret is called for. A dose of virtue ethics might make them concentrate more on how they should respond, rather than resting content with the thought that they have made the right decision (Hursthouse, 1999, p. 48).

Hence, the notion of patterns of practice links to virtue ethics not simply because of the way action can comprise a practice, but also because *how* we act—with regret, compassion, integrity, and so on—is conveyed by the notion: our patterns of practice include not only actions, but also demeanours and dispositions.

There is another subtle way in which a link can be made between virtue ethics and patterns of practice. To those who are not predisposed to virtue ethics as a normative theory this may seem contentious, and I suggest the link tentatively. While discussing religious practices I suggested that such practices are in some sense not just reflective of religious beliefs but constitutive of them. Similarly, it might be argued that moral practices do not just reflect ethical beliefs, but play a role in constituting them. There is something heretical in this because the normal presumption in medical ethics is that we use normative ethical theories to judge our actions, whereas I am suggesting that—in some albeit sketchy way—the normative simply emerges from the action. We might say that the normative is immanent.

Virtue ethics, it seems to me, squares with this view because it suggests the importance of what I *become* by what I do. It is as if we do not need the normative theory first, but rather the actions show us the possibilities for human beings. In an analogous manner, MacIntyre (1985), in his seminal study *After Virtue*, gave an account of the virtues that proceeded through three stages. The second and third stages considered the narrative unity of a whole life and the importance of an ongoing social tradition. But his account begins with practices. Other moral philosophers

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start with passions or desires or some conception of duty or goodness. But in such cases MacIntyre suggests,

the discussion is all too apt to be governed from then on by some version of the means-ends distinction according to which all human activities are either conducted as means to already given or decided ends or are simply worthwhile in themselves or perhaps both (MacIntyre, 1985, p. 273).

MacIntyre continues:

What this framework omits from view are those ongoing modes of human activity within which ends have to be discovered and rediscovered, and means devised to pursue them; and it thereby obscures the importance of the ways in which those modes of activity generate new ends and new conceptions of ends (MacIntyre, 1985, p. 273).

Once again, of importance here is what we become by what we do and the possibility that practices have the potential to enlarge our view of human flourishing. A key feature of the virtues is that they require a prior account of certain aspects of social and moral life in terms of which they can be defined and explained (MacIntyre, 1985, p. 186). The concept of a virtue requires a background against which it is made intelligible. The notion of a practice, which forms the first stage of the background, is defined by MacIntyre in a technical way:

By a 'practice' I am going to mean any coherent and complex form of socially established cooperative human activity through which goods internal to that form of activity are realised in the course of trying to achieve those standards of excellence which are appropriate to, and partially definitive of, that form of activity, with the result that human powers to achieve excellence, and human conceptions of the ends and goods involved, are systematically extended (MacIntyre 1985, p. 187).

The idea here is that, in order to pursue certain human goods, which help to constitute human flourishing, we have to engage in practices, where a practice itself aims at what is excellent for human beings. Football, chess, architecture, history, and medicine would all be examples of practices in this sense. Furthermore, according to this definition, such practices are patterned in a way that allows the possibility that they will reveal to us new and perhaps unexpected ways to flourish as human beings. From this virtue ethics perspective, the immanence of normativity is seen in the way that, within patterns of practice, conceptions of human goods are discovered and rediscovered through the actions of agents and by what they thereby become. Once a framework or pattern of practice is adopted there is a normative constraint on how things should go. The success or otherwise of a particular person engaged in a specific practice is not something that is open to subjective fiat. There is a normative constraint

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on what counts as excellence in a particular pattern of practice; but this constraint is internal to the practice; the normativity is quintessential despite ultimately depending on what people 'simply do'.

Thus, the notion of patterns of practice can be employed to do some difficult philosophical work in connection with thought and language as well as in the sphere of morals. I now come back to clinical practice, and to old age psychiatry in particular. The ethical question will always concern why one pattern of practice is better or worse than another. How do we justify community treatment over against in-patient admission? I do not intend to deal with this particular issue in detail, but merely to indicate the form of the argument. In order to do this, I require an overview of how patterns of practice are justified.

Justifying patterns of practice

The clinical problem is this: there may be different patterns of practice with respect to particular decisions. One community mental health team (CMHT) might try very hard to keep people in the community in their own homes for as long as possible. While this sounds laudable—it is what patients tend to say they would want and, therefore, it respects their autonomy—it does impose a good deal of stress on some family carers and there is always the risk that something will go wrong. The risk of self-harm is harder to manage in the community. Contrariwise, another CMHT tends to admit people very readily to an in-patient assessment ward. There are obvious concerns about this tendency in terms of cost, stigma, institutionalization, lack of respect for autonomy, the possibility of worsening behaviour learned from other in-patients, and dependence, not to mention the loss of liberty, especially if compulsion is required under mental health legislation. But, on the other hand, the admission might instantly de-escalate a tense situation for all concerned in the community and reduce the risk of violence towards self or others.

So, there are two patterns of practice. While I have said that the *clinical* problem is deciding between them, it is also an *ethical* problem: which pattern of practice is, from both the clinical and the ethical points of view, to be preferred? How do we justify one over the other? In passing it is worth noting that one way in which the notion of patterns of practice might be useful is *precisely because it brings together the clinical and the ethical*; and, in addition, it brings in the legal, the psychological, the social, the spiritual and any number of other potential aspects of a practice. Recall that MacIntyre (1985) defined a practice (in part) as a 'complex form of socially established co-operative human activity'. Whereas it is all too easy for there to be a discontinuity between clinical practice and ethical theory, or at best the latter is imposed on the former, the notion of patterns of practice inherently involves the complexity of clinical practice, whereby biological, psychological, and social considerations do not exhaust the possible levels of human involvement,

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which are likely also to involve ethical, spiritual, legal dimensions, and so on.

The other word used by MacIntyre (1985) in his definition of practice was 'coherent'. I argue that the coherence of a pattern of practice is the way in which it must be justified. This is to recommend a coherentist account of justification, which is often pitted against a foundationalist account. But recall that Wittgenstein spoke of 'bedrock', suggesting foundations, and then promptly appealed to a practice: 'this is simply what I do'. It might be that we do not need to enter further into this dispute: perhaps patterns of practice can be foundational, too, but they also require a mixture of internal and external coherence. Whether there is some 'ultimate' pattern of practice on which others rest and against which, therefore, judgments can be made when other patterns of practice clash, needs further consideration (Hughes 1995). But it is worth noting what Wittgenstein says in response to a question he puts to himself about judging the rightness of an action (where he is talking about obeying an order). He asks us to imagine ourselves as explorers in an unknown country with a strange language. He asks how in that country you would be able to judge whether orders were being given, understood, obeyed, and so on. Then he states:

The common behaviour of mankind is the system of reference by means of which we interpret an unknown language (Wittgenstein, 1953, §206).

This brings to my mind a picture of patterns of practice around particular words or phrases, with broadening patterns of practice as we expand to language and, finally, 'the common behaviour of mankind' when we start to think of language itself. And why should this picture not have some sort of application in the moral field? There may be local justifications for calling a particular practice virtuous, but in the end, we need something common: shared beliefs about what constitutes human flourishing.

Leaving the broader debate in favour of coherentism aside, I suggested earlier that there is a need for internal and external coherence. The first CMHT would be indulging in an internally incoherent pattern of practice if they strove to keep people in the community unless they lived in houses with yellow doors. The pattern of practice would be incoherent because it lacks consistency. If there were a good reason to discriminate against people in houses with yellow doors—if it signified a strange sect with a propensity to violence, for instance—then this consideration would need to be built into the complexity of the pattern of practice, which would thereby retain its coherence. Or, there could be different patterns of practice for people with yellow and non-yellow doors. More seriously, there might be different patterns of practice because of resources, depending on whether the crisis occurs on a weekday or over a weekend. This in turn raises the question about external coherence. Is the pattern

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of practice of the first CMHT better than that of the second? And is the weekend or weekday pattern of practice to be preferred?

Well, before moving away from these particular patterns of practice it might still be worthwhile to consider their internal coherence. MacIntyre (1985) spoke of 'co-operative human activity through which goods internal to that form of activity are realized'. The first CMHT needs to ask itself what the internal goods are at which its pattern of practice aims. The aim might be delineated by the virtue of respectfulness, in which case the CMHT would need to assure itself that variations in its pattern of practice (e.g. in response to weekends or yellow doors) still conveyed appropriate respect towards the person. If we imagine that they have to admit that they simply cannot strive towards respect at weekends, then to this extent they lack internal coherence. This internal incoherence will need to be weighed up against the putative coherence of the second CMHT, who always aim at both benevolence and fidelity: doing good and staying true to their patients. Of course, it can be questioned whether you always do good to people by pursuing a pattern of practice that inevitably leads to in-patient admission. But this is again to stress internal coherence. Here I have been gesturing at the possibility of external comparisons of internal coherence.

True external coherence comes when we ask how this particular pattern of practice squares with our other patterns of practice, or with the patterns of others. We must judge coherence within a broadening field, finally against something akin to 'the common behaviour of mankind'. For instance, a pattern of practice that encouraged compulsory admission would have to be squared with those other practices that valued liberty and autonomy. A pattern of practice that compelled psychiatric admission and treatment on those with political views at variance with the state would have to cohere with those patterns of practice that foster democratic rights and justice, or show them to be incoherent. By implication there is a connection—made by the interconnecting and overlapping of our patterns of practice—between an inclination to admit someone to a ward against their wishes and the pattern of practice embodied in our politically democratic institutions. Obviously, there is no easy way to compel a regime (or a person) to check its own patterns of practice against others, but this refusal to openness itself represents a pattern of practice that would be repudiated by other human practices. The iterative process of checking our patterns of practice for internal and external coherence might itself be regarded as a manifestation of human flourishing.

For the sake of external coherence, the inclination to use compulsory treatment should be modulated by our libertarian values. The weighing up of these different values can occur as an overt comparison between patterns of practice. More likely the process of balancing and assessing occurs naturally within the broad patterns of practice that constitute our clinical and ethical lives. When values are shared between patterns of practice, there is no incoherence; but when values diverge, we have to

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look elsewhere in order to figure how our patterns of practice might cohere. Thus, the business of assessing coherence between patterns of practice aligns with VBP: both reflect how in real life we must deal with diversity.

Clinical practice inevitably involves negotiating between values and navigating between patterns of practice. The aim is to find a way through and, according to the line I have been pushing, the form of the argument will always involve looking at patterns of practice for internal coherence and checking that any particular practice coheres with our broader patterns of behaviour and demeanour. In short, we justify particular cases by reference to our broader forms of life. And, inasmuch as these broader patterns of practice constitutively express the aims and aspirations of human beings generally, inasmuch as they manifest an essential normativity, they can be regarded as embodying something given for human beings like us.

What has to be accepted, the given, is—so one could say—*forms of life* (Wittgenstein, 1953, p. 226).

Summary

I have suggested that the notion of patterns of practice provides a useful way to think about ethical decision-making. I have suggested that this notion is useful both as a way to justify particular practices and as a way to uncover the connections between moral decisions and deeper philosophical concerns about the constitutive nature of normativity in our lives. Not only, therefore, might patterns of practice be clinically useful as a way of situating our ethical decisions and judging them for coherence, but also, through reflecting on patterns of practice, our ordinary clinico-ethical decisions are located in the broader patterns of human life.

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The scope of ethical issues

A wide range of ethical issues can occur in the practice of old age psychiatry. In the world of dementia, we have the benefit of a systematic review to highlight the ethical issues that seem to be specific to dementia (Strech et al., 2013). In this section I discuss some of the issues that emerge from the review using vignettes, which are fictitious but are (mainly) based on real cases. I do not, however, limit the discussions to dementia, but I draw on the notion of patterns of practice to see if this is helpful. The point to note about patterns of practice is that they are automatic: this is simply what we do. This does not mean that there is no rational basis to what we do, but the basis is inherent in the practice in terms of its internal and external coherence.

Case study 2 Early diagnosis

Background

Mr Able's wife was worried that her husband might have Alzheimer's disease. He is 52 years old and is self-employed. He is aware that it takes him longer to remember names and even that he has some difficulties recalling words, but he's not otherwise worried. However, both of his parents developed symptoms of dementia when they were in their 70s. His father died from a heart attack, but his mother lived on into advanced dementia and ended her days in a care home in a very dependent state. This worries Mr Able, so he finally agrees to visit his GP. He is given some tests. Aware that he made one or two errors, he is nevertheless a little surprised when he is referred to the local memory clinic. There he undergoes further assessments, including a brain scan. At the end of the process he's told that he has mild cognitive impairment (MCI) and that he should come back the following year.

Comment

According to many people, Mr. Able has done the right thing: he has sought diagnosis early. Furthermore, the system has worked effectively and he has been given the diagnosis of MCI. He will be followed up and can be given treatment and advice when the time is right. He can already be given advice about a healthy lifestyle and perhaps about making advance directives, and so on. The practice described here has a certain internal coherence. Early detection and management is the way to go!

It is, however, worth noticing that the diagnosis of MCI—in line with the principles of VBP—is not value-free (see Hughes and Williamson, 2019, pp. 123–6). It is not automatically true that a diagnosis of MCI will be helpful—indeed it may be harmful—partly because of the uncertainty. The label of MCI can be distressing (Corner and Bond, 2006). It needs to be recognized, too, the extent to which it is a social construct (Moreira, et al., 2008). With respect to MCI we can see values diversity. To some extent, at least, it may represent a good example of the medicalization of normal ageing. But, there again, some people regard ageing as a disease that needs be treated (Nuffield Council on Bioethics, 2018).

The system that views the management of Mr. Able as appropriate, therefore, could be regarded as—from at least some points of view—prone to a lack of external coherence if put into practice without careful consideration. There needs to be a good deal of practical wisdom shown. Compassion requires that the individual's values should be taken seriously and considered carefully. Emotional intelligence, genuine warmth, hopefulness, humble propriety, and a host of other virtues (see Box 51.2) need to be in evidence if things

are to be handled well for Mr. Able. How we impart an early diagnosis or a diagnosis of MCI will be crucially important. We may do these things automatically—and we may do them well or badly—this will be our pattern of practice. But whether that practice is good or bad, right or wrong, will depend on the external coherence of the values and dispositions (the virtues) that underpin our routine practice. There is at least a danger that we might get things wrong, whatever the scientific justification.

Case study 3 Biomarkers and early diagnosis

Background

Winning a large research grant is always exciting. Professor Klemperer's team has been working on the biological basis of Alzheimer's disease (AD) for some years. Now it's possible to look at normal middle-aged adults with and without a family history of dementia to screen for a variety of biomarkers that might indicate a risk of AD. The biomarkers are accessed via blood samples, cerebrospinal fluid, and neuroimaging. The neuroimaging includes a PET scan looking for amyloid. By chance, Professor Klemperer's nephew put himself forward as a control subject. However, when the results came back the nephew was positive for all of the biomarkers. Most alarmingly, his brain seemed to have significant amyloid deposition. The data was anonymised once the research team had it to hand and the protocol specifically said that participants would not have their results fed back to them. Professor Klemperer was bound by these rules, but felt terrible knowing that his sister's son had AD pathology even though he did not yet have dementia.

Comment

Professor Klemperer is abiding by the protocol submitted to the Research Ethics Committee. His actions are internally coherent. Incidental findings on imaging is a topic that has been given considerable thought (Royal College of Radiologists, 2011). Participants in studies are standardly told about incidental findings that are clinically significant and best practice would ensure appropriate support. In Professor Klemperer's study, however, the positive findings of Alzheimer's pathology in his nephew was not expected (in the absence of the family history), but was covered by the protocol. Because there would be no effective treatment, despite amyloid pathology, there seemed no good reason to worry participants with uncertain information about an uncertain future. Studies have looked at the effects of telling people that they are positive for biomarkers, but the issue deserves further ethical deliberation (Hughes et al., 2017). As in the case of Mr. Able (i.e. in connection with early diagnosis), therefore, undertaking studies of

prodromal dementia requires careful thought. The ways in which we do this (i.e. our patterns of practice) can usefully be subjected to analysis in terms of external coherence: to what extent does the practice cohere with the virtues that should inform and underpin actions? Does the practice of either telling or not telling someone of their biomarker status allow appropriate fidelity and respect for the person and demonstrate moral integrity and leadership (see Box 51.2)?

Case study 4 Families, autonomy, and confidentiality

Background

Mrs Sharma has been noticeably confused since her husband died, but she refuses to acknowledge that there is a problem. She says she is just getting used to life without him. But she seems to be putting herself at risk, sometimes wandering over to the park in the evenings, as she used to do with Mr Sharma. She is also ringing her family multiple times every evening, but still resists their offers of help. Her daughter, Nitya, takes her mother to the GP, but Mrs Sharma will not allow her to accompany her into the consulting room. Nitya rings the GP when she gets home, but the GP will not discuss Mrs Sharma with Nitya without her mother's permission, which the GP does not have.

Comment

This is a real bone of contention for carers of people with dementia. In the early stages they can, in effect, be told to get on with looking after their relative in the absence of any information about what is going on, all in the name of patient confidentiality. This would seem to be a practice with strong internal coherence. It coheres with the general practice of keeping confidential information confidential, which holds sway in all other branches of medical practice (in the absence of a threat to public safety and the like).

On closer scrutiny, however, cases like Mrs Sharma's may not be fairly compared with cases of, say, cancer or a multitude of other illnesses. When a person with cancer says she doesn't want her relatives told the diagnosis, this confidence is maintained. But this is because the person with cancer is deemed to have the capacity to make this decision. Even if the clinician feels that it would be beneficial to tell the family, she must not unless she has explicit permission. In the case of someone like Mrs Sharma, if it is true she does not recall that she is ringing her family all the time, it can be argued that she does not have the capacity to make a decision about her family's involvement with what is happening (Nuffield Council on Bioethics, 2009: para. 12). A decision would then have to be

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made in her best interests concerning whether or not to inform Nitya about Mrs Sharma's diagnosis and management. Internal coherence, therefore, requires that presumptions should not be made. This also has the benefit of supporting the family and other carers of the person. A pattern of practice that involved simply refusing to speak with any relative would be wrong. It would fail on grounds of internal coherence, but would also fail in terms of external coherence partly because of its lack of compassion for those who support the person living with dementia.

Case study 5 Advance care plans

Background

Mr. Moloznik always said that if he had severe dementia, he would not wish to be kept alive. Now he has advanced dementia, but he's been surprisingly happy for a long time. He seems to enjoy life. Indeed, he seems happier to be with people now than he ever did when he was younger, before his dementia. Many years ago, he and his wife made Enduring Powers of Attorney (EPAs) in favour of their daughter, Betty. Mr. Moloznik has now developed a chest infection. Before the family can stop it, he is admitted to the nearest hospital and the doctor wishes to give him IV antibiotics. Betty says that she does not wish for this to happen, but it is pointed out to her that an EPA only covers decisions relating to finance and property. The newer Lasting Powers of Attorney can cover welfare issues, including health decisions. But as things stand it is a medical decision as to whether Mr. Moloznik receives antibiotics.

Comment

Once again, the process of VBP would seem to be helpful. It would place Mr. Moloznik centre stage, but would ensure that all of the relevant facts and values were heard. Not to listen to Betty's views seems strange (if not shocking), especially given that she is the donee of the EPA and so was obviously someone that Mr. Moloznik trusted. In any case, given that he lacks the relevant capacity, a best-interests judgment should be made (in keeping with the MCA which covers England and Wales) and should involve 'anyone engaged in caring for the person or interested in his welfare' (MCA, s4(7b) and see Chapter 52). In addition, particular attention should be paid to Mr. Moloznik's past wishes and feelings, because we know that he said he'd not wish to be kept alive. This does not inevitably mean that he should now just be left to die! But it might be that, weighing everything up, including the fact that he's seemed to have a reasonable quality of life recently, it might have been decided to

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keep him in the care home and to try to give him oral antibiotics if possible, avoiding the hospital admission for IV treatment.

To demonstrate internal coherence, the doctor in this case would have had to say that he or she never listened to the views of close family members, or at least not if it was potentially a question of life or death and the family were on the side of 'allowing nature to take its course'. Although this somewhat extreme position would show internal coherence, it would fail on the grounds of a lack of external coherence, because it would not show compassion, nor fidelity to the patient's wishes, nor practical wisdom (that oral might be preferable to IV medication on this occasion, with room for the decision about treatment to be reviewed). In any case, most doctors would not take the extreme position and, I would suggest, this is precisely because it would not cohere either (internally) with their other practices or (externally) with the demands of the virtues that shape a good life.

Case study 6 Resource allocation

Background

Mr De Paul has had a diagnosis of schizophrenia for about 40 years. The community psychiatric nurse (CPN) has been visiting every two weeks to give him a depot injection of medication, which seems over the years to have kept his symptoms at bay. He is 73 years old and lives on his own. The CPN's manager is now questioning why other arrangements cannot be made to save the expense of the frequent visits. Possibly the injection could be given by one of the health visitors from the GP's surgery, who visits in any case to monitor his diabetes. Or perhaps he doesn't still require the injection given that there are now safer medications which can be taken by mouth.

Comment

The CPN is concerned about the therapeutic relationship that he has built up with Mr. De Paul. It would be reasonable to point to the risks of relapse and readmission to hospital, which would themselves involve considerable costs. It could further be pointed out that some of the 'safer' newer antipsychotics must be used with caution in people with diabetes. So, there are a number of arguments in favour of the status quo, but a number of arguments against it. These could be regarded as empirical details that could, in principle, be sorted out. This would be an example where the utilitarian approach might seem to fit, albeit there are imponderables, such as the likelihood of a relapse in this particular case.

Of course, if there were a sense that this saving was being imposed on against grounds, then there would be greater reasons to resist.

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This would be because of a lack of justice. It would, in part, then, show a lack of coherence with other practices, where people of a younger age were treated differently for no apparent reason other than their age. But the issue of justice is also a matter of external coherence, where social justice requires that practices are implemented with fairness, compassion, and integrity across society at large.

The issue here might be one of a lack of regard for the person. Ethical theories such as consequentialism can be criticized for their lack of attention to the individual. Virtue ethics, on the other hand, makes a virtue of partiality! There is a demand that we see ourselves as interconnected in ways that mean the person in front of you should appropriately command your attention and respect. Criticizing theories such as utilitarianism, Michael Stocker put it this way:

What is lacking in these theories is simply ... the person. For, love, friendship, affection, fellow feeling, and community all require that the other person be an essential part of what is valued. ... The defect of these theories in regard to love ... is not that they do not value love (which, often they do not) but that they do not value the beloved (Stocker, 1997: pp. 71–2).

The inclination of the CPN to continue to see Mr. De Paul—this pattern of practice—may well be motivated by the more or less conscious concern—love even—felt for him as a person. The need for this sort of external coherence is not a bad motivating force. At the very least, if the demand for efficiency wins out, handing on the care of Mr. De Paul is likely to be pursued in a better fashion if ‘love, friendship, affection, fellow feeling, and community’ hold more sway than might otherwise be the case.

Case study 7 Driving

Background

Bir Kaza has a diagnosis of bipolar affective disorder made in his late middle age. He has not tolerated lithium and refuses to take any other form of mood-stabilizing drug. He mostly seems to be a little high, although this could be put down to eccentricity. When he is obviously high it is sometimes possible to persuade him to take an antipsychotic drug for a couple of days. He is on an antidepressant at a low dose permanently. He relies on his car to get him to the shops and to the GP's surgery. Today he is high in his mood. He visits his GP, Dr Siradan, who tries to persuade Mr Kaza to take medication, but he refuses. When Mr Kaza goes into the car park, he reverses into Dr Siradan's car. The GP is watching from the window

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with horror. He immediately calls the Driver and Vehicle Licensing Agency (DVLA) and tells them he doesn't think Bir Kaza should be driving.

Comment

Issues around breaking confidentiality in connection with driving are well covered by General Medical Council guidance (2017). Dr Siradan has not complied with the guidance in that, apparently, he has not spoken to Mr Kaza about his driving and yet he is now speaking with the DVLA without warning him. But we are lacking details that might mitigate the GP's actions. For instance, it may be that the driving was very clearly reckless, as opposed to just a little careless. It might also be that the GP feels Mr. Kaza is so significantly manic as to be lacking in capacity to make decisions for himself about contacting the DVLA, and so forth (but in which case, perhaps he should have arranged a Mental Health Act assessment).

Dr Siradan's pattern of practice could be criticized because he might not have behaved in this way with another patient who did not have mental illness. In other words, perhaps the diagnosis of a mental illness has overshadowed judgments about the patient. A small prang in the car park might have been dealt with in an alternative way in a younger patient without a mental illness. So, the practice lacks internal coherence. And it shows, perhaps, a lack of the compassion, justice, temperance, and fidelity (see Box 51.2) that would allow the practice to have external coherence.

Case study 8 Sexuality and intimacy

Background

Mr Jones has marked dementia and lives in a care home. When the carers go into his room in the mornings to help him get ready, he is frequently found masturbating. He does not stop when he sees them. He laughs when they express alarm or consternation, which makes them think he is doing this deliberately. He has also asked staff to do it for him. Now he has been found masturbating in the lounge and one of the female residents has complained to her family who have seen the manager and asked that Mr Jones should be removed from the home, saying it's disgusting.

Comment

You sometimes hear it said that death is the last taboo; but it seems plausible to argue that sexuality in older people with dementia might be. The casuist line that we have been gesturing at in connection with the internal coherence of patterns of practice is applicable. Casuistry is about looking at things case by case, about immersing

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yourself in the details of the case, and about comparing difficult cases with paradigm cases, as well as about applying relevant moral theories (Louw and Hughes, 2005). Looking for internal coherence amounts to casuistry. A question in connection with Mr. Jones's case, therefore, is how would it be dealt with if he did not have dementia? Or, what if the behaviour that was giving offence was not sexual? These questions are not asked to excuse him, but to shed light on the coherence of our responses to him. Attention must be paid to the feelings and sensibilities of other residents as well as to those of the staff. But a natural thing would be to speak with Mr. Jones about the behaviour. This may not have been tried. Punishing him would not seem to be appropriate because, after all, he does have rights in relation to his private life and the home should be affording him both privacy and dignity. It may be that there are practical steps to be taken: leaving him to sleep for longer, giving him periods of time to be alone in his room at certain times of the day, engaging him with more meaningful activities at other times of the day, and so on. Staff need to treat this as they would any other type of behaviour that is challenging if their practice is to be coherent.

But there is a broader issue to do with our needs for intimacy and relationships (Hughes et al., 2014). Sexual behaviour in people with dementia must not always be dealt with solely as if it is a matter of capacity and safeguarding. External coherence might involve broader notions relevant to intimacy, such as friendship, compassion, charity, fulfilment, understanding, and so on.

Case study 9 Assistive technology and robots

Background

Ms Futuro received the diagnosis of dementia in 2032. She has been kept fairly stable by the mixture of medications that she has been receiving, but she does have mild to moderate cognitive impairment. This, together with her mobility problems, which her doctor said she had to accept at the age of 108, has started to make it difficult for her to continue to live independently. Luckily, her son has been able to buy a robot for her that will remind her of some day-to-day routines and can prompt her with certain tasks. It will also bring things to her, dispense her tablets, and monitor her movements so as to alert a controller if she runs into problems. Ms Futuro likes the robot, but she wishes she could see more of her son.

Comment

It may be that robots and assistive technology will turn out to be the way to care for the increasing numbers of older people in the world. We shall have to see! But we also need to be asking the right

questions as the technology develops. To what extent do these developments square with (show internal coherence with) our other practices of care where the emphasis has been on person-centredness? To what extent does an emphasis on technological care square with (show external coherence with) our notions of the good life, of a life that can be lived well and exhibit, insofar as possible, human flourishing? The move, in thinking about assistive technology, has been away from concerns about privacy to concerns about loneliness (Hughes, 2014).

Case study 10 Truth-Telling

Background

Verity always wanted to work with older people. Now she is a care assistant in a care home. There is a particular older woman called Mabel, who is visited every day by her devoted husband, Otto. Verity has formed a bit of a bond with them both. She then hears from the family that Otto has been taken ill and is in hospital. Mabel is told this and, although she has been vague about who Otto is recently, she becomes noticeably upset by the news. She does not seem to be able to remember the news, but she does ask where the man is, which is how she refers to Otto. Two days later, Verity hears from the family that Otto has died. But the family say that Mabel must not be told, because it would upset her unnecessarily and she would not remember anyway. They say she should just be told that he's visiting tomorrow.

Comment

Verity may well feel a sense of tension. Her general style is to be honest with everyone. It will be difficult for her to tell a blatant lie, but she would generally wish not to upset the family, especially not at this difficult time; and she's been told that she must do as they wish. Verity's pattern of practice, to maintain a sense of coherence, has to negotiate her inclination to tell the truth with her inclination not to upset anyone. This shows how internal coherence and external coherence coalesce at times. Verity's other practices tend to be truthful; the external demand, as part of human flourishing, for honesty also influences her practice.

Luckily, we can think of a spectrum from full truth to outright lies. Perhaps the full truth will sometimes not be possible, even if it should always be the aim of professionals. But there are techniques such as distraction and changing the subject which avert the need to lie and avoid upsetting someone (Williamson and Kirtley, 2016). Nevertheless, it is also not unlikely that Mabel will accept the truth much more readily than the family believe, that she will be more

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unsettled without the truth, and for these reasons, they should be gently encouraged to try to tell her the truth at a suitable moment. Not to do so may be to undermine her standing as a person and not demonstrate the sort of respect she deserves as a matter of charity and fidelity.

Case Study 11 Antipsychotics and behaviour that is challenging

Background

Since his admission, Jock has been pacing around the assessment unit for people with advanced dementia clearly looking for a way out. When staff try to distract him, he becomes aggressive. This has only been verbal aggression, but last night he was again trying a door when another male patient walked past and Jock suddenly hit him. The team are now considering whether or not Jock should be prescribed an antipsychotic.

Comment

The management of behaviour that is challenging in dementia is covered in Chapter 19. The counsel of perfection is to use nonpharmacological means first, before drugs, unless the situation is dangerous. The point I wish to draw out here is that we (as prescribers) have a strong inclination to use medication because we know that it will work quickly, whereas other methods will take some time to work, if they will at all. But we need to recognize that this inclination may not cohere with inclinations elsewhere in our practice. It might well be that for a mild depression we would always recommend psychological approaches first. Even if this is not the case, we still pay lip service to the importance of evidence-based medicine. The evidence tells us that prescribing antipsychotic drugs for people with behaviour that challenges is not the most appropriate treatment here (even if it might be under other circumstances). So, there is the potential for a lack of coherence in our practices. In addition, the requirement that we should put into effect person-centred care should also encourage a broad view, based on a broad view of the person (Hughes and Beatty, 2013). External coherence, therefore, involves fidelity to the person, as well as charity, integrity, perseverance, and so forth (see Box 51.2).

Case Study 12 Covert medication

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Background

It is decided to give Jock an antipsychotic. The difficulty is that he refuses to take it. It's suggested that they might give it to him covertly, by crushing it into copious jam in his sandwich, which he loves. Some staff are uneasy about doing this, but they've been told that it is legal when done in his best interests.

Comment

There are guidelines and established principles for giving covert medication. Treloar and colleagues (2001) felt covert medication was acceptable under exceptional circumstances. This seems right, but (of course) a judgment is then required about what is exceptional. If it is likely that a person's health will decline unnecessarily without covert medication, then this would seem like the exceptional circumstances required to justify its use. The internal coherence will be with practices that are beneficent and nonmaleficent. But there can hardly be coherence with the principle of respect for autonomy. External coherence, therefore, must support the practice despite the loss of autonomy. Virtues such as trustworthiness, realism, practical wisdom, compassion, and so on (see Box 51.2) will be relevant.

Case Study 13 Forced care

Background

Margaret screams every time she is taken for a bath. She fights the staff. They feel that they cannot force her to wash. So, they adopt a policy of offering her a bath every other day, but they don't push the issue in case she gets aggressive. However, Margaret has double incontinence and needs to be changed several times a day. It is always a struggle and she always resists. They are not able to clean her properly, but they feel this is all they can do given that she is not able to consent to such treatment and they are concerned it would look like assault if they insisted she bathed. The difficulty is that she is becoming smelly. Other residents do not wish to be near her. They are calling her names. Her poor hygiene is also putting her skin integrity at risk.

Comment

The issue here is that the care Margaret requires increasingly must be given, but she strongly resists. So, the care must be given forcibly. The staff are not keen to do this because they feel it is against legal and ethical guidance. In other words, they are aware of

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a tension in terms of their normal patterns of practice. Normally they seek consent or cajole, but they do not force.

The reorientation required is to see that their inclination to care actually does cohere with the practice of providing 'forced' or necessary care; and can also be legal (Jackman et al., 2014). The key thing is that they should provide such care in accordance with best practice: only using force when it is absolutely necessary, documenting their reasoning behind the use of force, still showing respect to Margaret and protecting her dignity, using enough staff so that it can be done effectively, safely, and swiftly. Under these conditions, 'forced' care can also cohere with the appropriate virtues (compassion, charity, patience, and the like) that underpin all good-quality care.

Case Study 14 Withholding and withdrawing

Background

Mr Bolus, who is in the terminal stages of his dementia, has started choking almost every time he is fed. His son, who lives in America, has suggested by email that his father should be given a percutaneous endoscopic gastrostomy (PEG) tube through which he can be fed. The staff looking after him are not in favour of this and nor is his daughter. She, however, still wishes for him to be fed. At the same time, it is being questioned whether he still needs to receive all of the medication that he previously took. First, he cannot swallow the tablets. Secondly, it is not obvious that they are of benefit to him. Some staff feel it would be better if he were to die.

Comment

First, we need to pay attention to the relevant evidence and, such as it is, this suggests that PEG feeding is not worthwhile (Sampson et al., 2009); secondly, we need to keep in mind the tenets of VBP and acknowledge the diverse values that are in play around the feeding of Mr Bolus. The same impulses that make us not want to use a PEG tube, because it will not do him good and may do him harm, also make us want to stop his unnecessary medication. This shows internal coherence in our patterns of practice. But we still wish to feed him and judgements about the risks and benefits make us believe that oral feeding is still worthwhile, partly because of the human contact it brings. Despite the increasingly difficult circumstances for Mr Bolus, there is a pattern of practice—to do with feeding him appropriately despite the risk of choking—which coheres (externally) with virtues such as empathy, justice, moral integrity, practical wisdom, respect for personhood, and self-effacement. Meanwhile, as in many end-of-life situations, the

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doctrine of ordinary and extraordinary means applies: we must do the ordinary things, but are not morally obliged to do the extraordinary, where 'extraordinary' is defined as actions which are unlikely to work and are likely to be burdensome.

The feeling that it would be better if Mr. Bolus were to die is perfectly understandable. The doctrine of ordinary and extraordinary means allows us not to pursue every means possible to keep someone alive. However, this feeling has for many people turned into support for euthanasia or for physician-assisted suicide. Deliberately aiming at the death of patients does not, in my view, cohere with the patterns of practice that should characterize good medical care. The argument in favour of killing patients is that it can show respect for autonomy, but there is no reason to consider autonomy an overriding principle. Fuller discussion can be found elsewhere (Hughes, 2010; Hughes, 2013). And doctors should note the Statement of the World Medical Association (accessed 4 February 2018):

Physician-assisted suicide, like euthanasia, is unethical and must be condemned by the medical profession. Where the assistance of the physician is intentionally and deliberately directed at enabling an individual to end his or her own life, the physician acts unethically. However, the right to decline medical treatment is a basic right of the patient and the physician does not act unethically even if respecting such a wish results in the death of the patient. [<https://www.wma.net/policies-post/wma-statement-on-physician-assisted-suicide/>]

Conclusion

This chapter has explored a number of different moral theories and approaches and highlighted VBP. It has also introduced the notion of patterns of practice and shown its relevance to everyday practice in old age psychiatry. This is despite the variety of ethical issues that arise. In conclusion, I repeat a quote from the philosopher Michael Luntley, which in some sense sums up the attitude I've been, however shakily, seeking to sketch: 'The moral world has its being in, it rests upon, what we do and how we act. It is in our actions and the way we treat one another that values come into being and are preserved in being' (Luntley, 1995, p. 218).

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Mental capacity and decision-making

Chapter: Mental capacity and decision-making

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Introduction

In 1998, American psychiatrists Thomas Grisso and Paul S Applebaum made the following observation in their text: *Assessing Competence to Consent to Treatment: A Guide to Physicians and Other Officials*:

Competence is a pivotal concept in decision-making about medical treatment. Competent patients' decisions about accepting or rejecting proposed treatment are respected. Incompetent patients' choices, on the other hand, are put to one side, and alternative mechanisms for deciding about their care are sought. Thus, the enjoyment of one of the most fundamental rights of a free society—the right to determine what shall be done with one's body—turns on the possession of those characteristics that we view as constituting decision-making competence (Grisso, T. and Applebaum, P. (1998) *Assessing competence to consent to treatment: A guide for*

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physicians and other health professionals. Oxford University Press, p. 1).

What Professors Grisso and Applebaum are describing here is the idea that mental capacity, or competence as they term it, acts as a gateway to personal autonomy in medical decision-making (Donnelly, 2010; Beauchamp, 2013). In most western legal systems, competent adults are free to make significant health, welfare and financial decisions—even unwise decisions—which are, by and large, respected in law. By contrast, those who lack decision-making capacity can have their express wishes overridden by others, acting in their perceived ‘best interests’. Mental capacity exists, therefore, as a boundary or threshold concept in law, distinguishing those who have the right to make autonomous decisions and to carry out legally significant acts from those who do not (Richardson, 2010).

Specialists in old age psychiatry are frequently called upon to assess capacity in relation to medical treatment decisions, determining living arrangements, and a range of other contractual and financial matters relevant in older people’s lives. Issues of capacity and impaired decision-making are particularly prevalent in old age services; this is largely because older people are more likely to have chronic physical and mental health problems that may directly compromise their decision-making ability (Moye et al., 2013). The success of modern medicines and life-sustaining interventions, particularly in the tertiary health sector, has meant that older people’s lives can now be prolonged for many years, even after their cognitive abilities have become impaired, or totally obliterated, by underlying disease or trauma (Buchanan and Brock, 1990). The effects of stroke, infection, coma, the side-effects of medicines, learning disability, dementias, psychosis, and other forms of mental disorder and mental illness, can all have the potential to impact upon an older person’s cognitive functions and consequent capacity in later life.

When significant health, welfare, and financial decisions are proposed, it is usual for health, social care, and legal professionals to be tasked with determining who sits above or below this capacity threshold. Accordingly, these professional gatekeepers wield great power. If an older person is judged to lack capacity, this can have profound and often enduring impact on that person’s freedoms. If, for example, we were to find that Mrs Jones lacks the required capacity to remain living at home and should move into a nursing home, we would be taking away her legal agency, in the sense that her right to choose where she lives and her ability to act on that choice may no longer have legitimacy or legal consequence. We would also be removing, or at the very least diminishing, her sense of personhood, and her social standing as a rational, competent human being. So, it follows that the way we determine capacity and make best-interests decisions must be carefully considered, because if our judgements are not legally and ethically defensible, we can arbitrarily

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deny people their rights of self-determination and liberty, which are fundamental human rights.

In this chapter, we focus on the concept of mental capacity, how it is assessed, and its relevance to old age psychiatry. We consider the legal consequences of incapacity, both for the older person concerned and others, before moving to look at some broader principles governing the use of restraint, deprivation of liberty, and support for decision-making. Finally, we turn our attention to how international human rights legislation, and the international disability rights movement generally, increasingly shape the legal approach to capacity and decision-making in the UK.

Although our discussion in this chapter focuses primarily on the *Mental Capacity Act 2005* (MCA), which is the legal framework governing decision-making for those who lack capacity in England and Wales, we have also referred to the *Adults with Incapacity (Scotland) Act 2000* (AISA), which provides an equivalent, albeit very different legal framework in Scotland. We also make reference to the newly enacted *Mental Capacity Act (Northern Ireland) 2016* (MCANI) which takes a radical break from the traditional approach to mental health treatment adopted in mainland UK by ‘fusing’ mental health and mental capacity laws. Once the Act comes into full force in Northern Ireland, mental health treatment in all cases will be based on consent or a lack of decision-making capacity. In this way, the legislation seeks to minimize the stigma associated with compulsory treatment for mental disorder and places the person concerned at the centre of decision-making. The Law Commission has urged the UK and Welsh Governments to consider introducing a similar capacity-based approach in England and Wales in any future reform of mental health law (Law Commission, 2017b, (13.18)).

What is mental capacity?

At its simplest, mental capacity suggests the ability to make a decision, or to perform a task (Culver and Bernard, 1982). This characterization of capacity as an *ability* suggests something practical: that capacity involves practical knowledge, or knowhow (Hughes, 2014). We can see this approach reflected in the ‘functional’ test of incapacity under the MCA in England and Wales: it is the *inability* to understand, retain, and weigh relevant information, or communicate a decision, that indicates a lack of decision-making ability. When any one of these inability is caused by an impairment of, or disorder in the functioning of the mind or brain, then the test of incapacity is satisfied. To this end, the statutory test appears relatively straightforward. However, there are inherent problems when it is applied in the real world of clinical practice.

First, capacity is not an objective scientific term that can be measured with forensic precision. Identifying whether a person lacks the required level of understanding to be deemed incapable of making a specific

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decision at a particular time requires rigorous medical and lay assessment and can rarely be stated in absolute or conclusive terms (Gostin, 1986; *Re T (Adult: Refusal of Medical Treatment)*, 1992). Lord Carnworth's rather lyrical view of incapacity from the 1857 case of *Boyse v Rossborough* serves to illustrate this point:

Between ... an extreme case (of mental illness) and that of a man of perfectly sound and vigorous understanding, there is every shade of intellect, every degree of mental capacity. There is no possibility of mistaking midnight for noon; but at what precise moment twilight becomes darkness is hard to determine. [para. 45]

Secondly, capacity can be unpredictable. A person's capacity to understand and retain relevant information may be intermittent, or fluctuate over time according to the effect of his or her illness or disorder (Law Commission, 2017a). Take Mrs Murray, who has vascular dementia; there might be certain times of the day when she thinks more clearly than others. Her capacity may fluctuate from hour to hour and from decision to decision. Equally, her decision-making abilities will depend on the nature of the decision to be made. She may be capable of making simple decisions about what to buy from the shops, but lack the capacity to deal with more complex financial transactions, like selling her property, or making her will. Her abilities will therefore vary according to the objective demands of the task in question (Buchanan and Brock, 1990).

To this end, the MCA favours a time- and decision-specific approach to capacity: capacity is assessed not in a general sense, but in relation to a particular decision to be made at a particular point in time (*Code*, para. 4.4; *A Local Authority v TZ* (2014) at paras. 24–25). The important consideration is whether, at the time a decision is required, or an act needs to be carried out, Mrs Murray has capacity to make that particular choice. To describe her as simply 'lacking capacity' in a general sense, in relation to all matters, would be meaningless in law (39 Essex Street, 2017).

So, by adopting a time- and decision-specific approach to capacity, we recognize that, although people may lack capacity in some aspects of their lives and need support, they are still able to act independently in others. It also becomes apparent that a capacity assessment will be difficult to do well if an assessor has no previous knowledge of a person's particular characteristics and routines, and how their physical and mental problems affect their decision-making capacity (Buchanan and Brock, 1990).

This leads to the related point that capacity is a 'value-laden' concept (Greener et al., 2012). While it might be tempting to view capacity as a test of a person's cognitive ability to weigh up factors, rationally, and to reach a logical conclusion about a singularly correct course of action, to do so would be to take a restricted view of capacity. Decision-making is heavily influenced by values, beliefs, and other relational and emotional

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factors that shape the way we weigh up information and make personal choices in life (Gibson, 2017). An interesting report published by the Joseph Rowntree Foundation (2012) on improving decision-making in the care of older people suggests that the decisions older people make are heavily influenced by relational and contextual factors and do not always reflect assumed notions of 'conscious rationality'. Hence, the way we judge another person's capacity should not ignore the 'situated perspective' of the individual being assessed (Hughes, 2014), but pay attention to any cultural, ethnic, or religious life choices which may influence their way of thinking, behaviour, and communication.

This also suggests that those assessing capacity must be alive to their own biases and prejudices and think broadly when making judgements about the abilities of others to make decisions. It is all too easy for unjustified assumptions to be made about an older person's abilities based on a person's diagnosis or age, or because of a desire to keep the person safe. Paternalistic practices can often result in older people being judged to lack capacity simply because they make decisions that are perceived to be risky, or contrary to an assessor's own value system (Wong et al., 1999; Emmett et al., 2013). This would adopt an 'outcome-based approach' to capacity assessment, which the Law Commission of England and Wales has rejected as it 'penalises individuality and demands conformity at the expense of personal autonomy' (Law Commission, 1995, (3.4)).

All the same, outcome-based approaches to capacity assessment appear a lot in practice (House of Lords, 2014). In many ways, this is understandable. If an older person, who might have a degree of physical or mental vulnerability, makes it plain that he or she wishes to choose a course of action that has the potential to lead him or her to harm, those who care might determine that the person concerned lacks the requisite capacity. Yet it is an approach which militates against accepting unwise decisions and respecting autonomous choices and for this reason should be avoided. After all, the purpose of the MCA's jurisdiction is to enable those who lack capacity to enjoy life to its fullest with the potential available to them; and to lead life to its fullest is, inevitably, to incur some risks (Hedley, 2014).

So, if we consider Mrs Murray again: she wants to remain living at home, she struggles with her continence, is unkempt, and her fridge contains out-of-date food. She says that she understands the risks of living at home, but would rather die on her own kitchen floor than in a care home.¹ In this situation, the temptation is to conclude that Mrs Murray lacks decision-making capacity, as her wish to stay at home in squalor might be at odds with our view of how she should live her life. Yet, by doing so we are making judgements about how she should live her life based on our own values; and by denying Mrs Murray her mental capacity to make her own choices about her living arrangements we are denying her the exercise of her human rights. So, this is not a step we should take

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lightly—and not without a conducting a careful enquiry into her capacity to make this decision.

Which brings us to the question of how capacity should be assessed.

Guiding principles of the MCA

The MCA begins at section 1 with a set of five guiding principles, or benchmarks, which must be applied to all acts and decisions taken under the Act. Principles 1 to 3 are particularly relevant to capacity assessment. The MCA's guiding principles are reproduced in Box 52.1.

Box 52.1 The principles of the Mental Capacity Act 2005 (Section 1)

The following principles apply for the purposes of this Act:

- 1** A person must be **assumed to have capacity** unless it is established that he lacks capacity.
- 2** A person is not to be treated as unable to make a decision unless **all practicable steps to help** him to do so have been taken without success.
- 3** A person is not to be treated as unable to make a decision merely because he makes an **unwise decision**.
- 4** An act done, or decision made, under this Act for or on behalf of a person who lacks capacity must be done, or made, in his **best interests**.
- 5** Before the act is done, or the decision is made, regard must be had to whether the purpose for which it is needed can be as effectively achieved in a way that is **less restrictive of the person's rights and freedom of action**.

Mental Capacity Act, 2005. © Crown copyright

The presumption of capacity

The starting point in any capacity assessment, and the first guiding principle of the MCA, is the presumption of capacity: 'A person must be assumed to have capacity unless it is established that he lacks capacity.' Just because someone has a diagnosis of a mental disorder or impairment, does not mean, of itself, that they are unable to make a decision and lack capacity.

Case Study 1

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John Thompson is a 45-year-old man with Down syndrome. There is a question as to whether he might now be developing dementia: there has been some deterioration in his ability to attend to his daily needs. He has been living for some years in a supported home with three other men with intellectual disabilities. The home now has to be sold and the charity which runs the home is looking for alternative accommodation for the four residents.

A first step we must assume that John has the capacity to decide his own living arrangements unless it is proven otherwise. In this way, we are much less likely to take away his right to make autonomous decisions. John may well have some strong preferences about the area he wishes to live in and about with whom he wishes to live. If he has the capacity, he should be allowed to make his own decision and we would not want to take away that right without a careful enquiry into his decision-making capacity. To assume that he lacks capacity without further enquiry would deprive him of his legal right to make a decision about where he lives as well as show him considerable disrespect: not only in general terms as a person, but also specifically in terms of his autonomy.

Equally, nothing should be presumed merely on the basis of John's diagnosis of Down syndrome, whether or not he also has dementia. This would assume a 'status' or 'category' approach to capacity based on John's membership of a particular diagnostic group. This is explicitly precluded by s2(3) MCA, which states capacity cannot be established 'merely by reference to a person's age or appearance, or a condition of his, or an aspect of his behaviour, which might lead others to make unjustified assumptions about his capacity'. Such an approach has also been rejected by the Law Commission as oversimplifying the question of whether a person has decisional capacity and undermining the respect for individual rights (Law Commission, 1995 (2.43)).

The onus is on the person who considers that it may be necessary to take a decision or step on John's behalf (the 'decision maker') to displace the presumption of capacity, on the balance of probabilities. It is not for John to show that he has capacity, but for the decision maker to show that, on balance (more likely than not), John lacks the capacity to decide his living arrangements. Also, care should be taken to reflect the correct standard and burden of proof in any record of the assessment made. In *Heart of England NHS Foundation Trust v JB* (2014), a case in which a patient with paranoid schizophrenia refused the amputation of a gangrenous foot—in terms of facts reminiscent of the well-known case of *Re C (Adult: Refusal of Treatment)* (1994)—Mr Justice Jackson stated in his judgment:

At all events, it is for the Trust to displace the presumption that JB has capacity on a balance of probabilities. It is important that the right question is asked. When assessing JB in October, Dr O approached matters on the basis that JB was 'unable to *clearly* show

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that she had considered the option' of amputation. Similarly, in January, Dr B remarked that 'one needs to *be certain* of her capacity' while in February, Dr O recorded that JB 'is unable to *fully* understand, retain and weigh information ... '. These formulations do not sit easily with the burden and standard of proof contained in the Act (emphasis added). [para. 27]

Turning again to John Thompson, and recalling that capacity is always task- and time- specific, we should question whether John has the capacity to make the particular decision that is required at the moment. If he does not, two questions follow. First, might he regain the required decision-making capacity? If it is reasonable to wait, then the decision should be postponed (s4(3) MCA). Obviously, if the decision genuinely cannot be put off, then it will have to be made for him; in which case we must act in his best interests. But before we get to that, the second question, which follows if John is struggling to demonstrate the level of capacity to make the particular decision required, concerns whether he might be helped to gain or regain the required capacity. This is the second principle of the MCA.

The supported decision-making principle

The MCA specifies at s1(3) that 'a person is not to be treated as unable to make a decision unless all practicable steps to help him to do so have been taken without success'. This is sometimes referred to as 'the supported decision-making principle' of the MCA and is arguably one of the most important principles of the Act, yet one that is often ignored in practice (House of Lords, 2014). Its purpose is to maximize capacity by enabling a person to make an autonomous decision wherever possible.

Given the importance of the principle, the new MCANI 2016 sets out concrete examples of what may amount to supported decision-making explicitly on the face of the Act at section 5, under the heading 'Supporting person to make—decision'. Under the MCA, ways of enhancing a person's capacity are to be found in the MCA *Code of Practice* at Chapter 3 (Department of Constitutional Affairs, 2007). These include making sure that the person has all the relevant information he needs to make the decision, including any options that might be available. Relevant information needs to be presented in a way that is easy for the person to understand, using pictures, photographs, videos, tapes, or sign language where appropriate. Relatives, friends, or advocates should assist with the assessment, if they are better able to help the person understand. Similarly, thought should be given to whether the timing and venue for the assessment are appropriate (Poole et al., 2014). Assessments should take place when the person is most likely to be functioning well—perhaps in the morning, or a period when an older person is known to be more lucid. Consequently, capacity assessments must not be conducted at random times on busy wards with frequent interruptions from other staff and distractions and noise.

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It is also worth reflecting on the meaning of 'practicable'. We are told that what are practicable steps to maximize capacity 'may vary depending on the decision to be made and the timescale for making the decision and the individual circumstances of the person' (*Code* para. 3.1). We might be tempted to regard some things as not 'practicable', because there is not enough time, because people are too busy, because it will cost too much money, and so on. These might be reasonable excuses and they might mean that a certain course of action is not 'practicable'. But the wording of the MCA is uncompromising: a person cannot be regarded 'as unable to make a decision *unless* all practicable steps' have been 'taken without success' (with the emphasis added). The clear implication is that all practicable steps must be attempted. 'Practicable' does not mean 'convenient'; it rather suggests that if it can be done, however inconveniently, it should be. That being said, 'practicable' does not mean 'possible', so it is accepted that what is practical will vary and compromises may have to be made. Much depends on the urgency and nature of the decision to be made and the circumstances or condition of the person concerned. Significant, one-off decisions (such as deciding upon a change of residence, or whether to undergo a serious medical procedure) may warrant greater efforts to maximize a person's capacity compared to day-to-day decisions about care and welfare. However, the same general processes should apply to each decision (see *Code*, para. 3.3).

Case Study 2

Mr Chan has severe Parkinson's disease and dementia. He is now unable to communicate, but requires a decision about his future care. The clinical team take the time required to involve the speech and language therapists to see if it might be possible to facilitate some form of communication. The speech and language therapists spend several sessions with Mr Chan trying to find ways to help. His Parkinson's medication is reviewed. He is seen by the old age psychiatry liaison team in case some feature of his mental state (depression or confusion) might be amenable to treatment but impeding his communication.

These are 'all practicable steps', which accordingly have to be taken, not just to comply with the law, but also because to do less than this would be to undermine Mr Chan's standing as a human being with rights, who is worthy of respect.

So, too, with John Thompson. The charity running the home in which he lived arranged for a team of specialists to see him over several weeks and months to try to understand his wishes about his future place of residence and care. They used pictures, and stories, held conversations

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with John as well as the other residents and staff, took John to look at several different areas and possible places to live, and reflected with him and with his family. Again, all practicable steps were taken to allow him to participate in the decision.

What prompts a capacity assessment and who should assess capacity?

If we believe that a person may have lost (some components of) capacity we have to be careful about how we determine whether this is true. We should, after all, presume capacity (see Box 52.1). Where there is a suggestion that capacity may be impaired, then there are grounds for making an assessment, without which the person may be vulnerable. By and large this will not create problems, if handled sensitively and appropriately.

There is often no one thing that prompts the need for a capacity assessment, although there are factors which, when considered together, may suggest diminished decision-making capacity. These signs should not be taken alone as proof of incapacity, but may indicate a need for further evaluation and assessment. So, any abrupt changes in mood or personality, confusion in time or space, difficulties completing familiar tasks, or where a person makes a series of unwise transactions or decisions which puts himself or others at risk, may be markers of declining capacity. Often family members and carers may be the first to notice these changes and may express concerns. When these indicators are coupled with the presence of an impairment or disturbance that affects the abilities of a person to decide, this may prompt a more detailed enquiry into their mental capacity.

It is widely acknowledged that capacity is more likely to be questioned in practice when a person disagrees with a proposed course of action (Shah et al., 2009; House of Lords, 2014). There is also evidence to suggest that people who do not question professional opinion might avoid an assessment of capacity altogether, even when there is cause to doubt the presumption of capacity (Okai et al., 2007; House of Lords, 2014). However, as previously mentioned, anyone who carries out an act or treats relying on an invalid 'incapacitated consent', or with no consent at all, would be acting unlawfully (*Re F (Mental Patient: Sterilisation)* (1990)).

Most often the professional who is directly concerned with the individual at any one time, and who proposes to carry out an act, or make the particular decision, will assess capacity as 'decision maker'. This person must have a reasonable belief that the person concerned lacks the requisite capacity before they can act lawfully in the incapacitated person's best interests. Occasionally, where there is a question over a person's capacity, where it is borderline or fluctuating, or where a decision is particularly serious or likely to be challenged at a later date, then assistance from a specialist psychiatrist or other medical

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professional might be sought (*Code*, para. 3.37). For example, a solicitor who needs to be satisfied that an older person has the requisite capacity to make a will, or create a Lasting Power of Attorney, may request the assistance of an old age psychiatrist when forming this opinion. In this situation, the consultant psychiatrist, as assessor, will be acting purely in an advisory role, with the decision maker (the solicitor) remaining the person who is ultimately responsible for the capacity decision.

Given that so many decisions need to be made in respect of an older person at any one time, it is likely that different decision makers will assess a person's capacity to make different decisions at different times throughout the day. Although a person's capacity needs to be assessed every time that person is required to make a decision, the formalities surrounding the assessment, and who should be the assessor, depend on the seriousness of the decision to be made, or the acts to be carried out. Professionals qualified in a particular field are normally expected to undertake a fuller assessment of capacity than family members or other carers who have no formal qualifications, reflecting their higher degree of knowledge and experience (Donnelly, 2009). For example, nurses and lay carers may make countless capacity assessments every day when caring for older people. These are made almost intuitively, without any formalities and it would be highly impractical to document these types of assessments against the requirements of the MCA on each occasion. Nevertheless, lay carers, like professionals, will still need to justify their objective reasons as to why they believe an individual lacks capacity if required to do so by a court.

The capacity test under the MCA

The Mental Capacity Act 2005 defines incapacity in the following way, at section 2(1):

... a person lacks capacity in relation to a matter if at the material time he is unable to make a decision for himself in relation to the matter because of an impairment of, or a disturbance in the functioning of the mind or brain (section 2(1)).

There are two distinct elements to this definition.

The first focuses on the person's inability to make the decision at the material time. This is known as the 'functional test' and centres on a person's decision-making abilities.

The MCA then sets out what it means to be 'unable to make a decision'; namely, the person is unable:

- 'To understand the information relevant to the decision
- To retain that information
- To use **or** weigh up that information as part of the process of making the decision, **or**

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-
- To communicate his decision (whether by talking, using sign language or any other means).’ (section 3(1))

The second element is that a person’s inability to make a decision must be ‘caused by an impairment of, or a disturbance in the functioning of the mind or brain’. This is commonly known as the ‘diagnostic test’. This impairment may be temporary or permanent and would encompass those who lack capacity following a physical injury to the head or body that results in confusion, or unconsciousness; those suffering from a confusion brought on by alcohol and drug misuse, severe pain, shock or fatigue; as well as the more obvious categories of psychiatric illness, dementia, or the long-term effects of brain damage.

It is important to stress that, according to the definition of incapacity under the MCA, the inability to make the decision must be *due to, or because of*, an impairment or disturbance in the functioning of mind or brain. The courts have referred to this as the ‘causative nexus’ that must exist between the inability to make a decision and the impairment of mind or brain. In *PC and NC v City of York Council* (2013) the suggestion by experts that PC’s inability to make the decision to cohabit was ‘referable’ to or ‘significantly relates’ to her mental disorder fell short of finding that the inability was ‘because of’ her disability as required by MCA s 2(1).

Of course, the tendency in practice is to approach capacity assessments by focusing first on the diagnostic threshold before moving onto the functional test—after all, this is what the *Code* advises us to do! However, the Court of Appeal in *PC and NC v City of York Council* suggested that this approach (focusing on the diagnostic test first) might mean that the ‘causative nexus’ of the test is ignored. According to McFarlane LJ,² we should instead ask whether the person concerned is unable to make a decision by applying the section 3 functional test first, before moving to ask whether this is because of the underlying mental or brain impairment. Whether this advice is widely taken up in practice remains to be seen, although it probably matters very little as long as the person’s diagnosis does not lead to an assumption of incapacity, or the causative nexus is not overlooked.

Information: How much and what needs to be understood?

When providing information, careful thought must be given to the nature of the decision to be made and the relevant legal test that might apply. In the UK, there is a variety of common law tests of capacity, which include tests for testamentary capacity, capacity to make a gift, to marry, or to litigate, and so on. These tests are not replaced by the MCA. Some, as in the case of testamentary capacity, hold sway in other jurisdictions too. These specific tests are well described in the excellent guide published by The British Medical Association and the Law Society, now in its fourth edition (British Medical Association and Law Society, 2016). In Scotland, similar BMA guidance can be found online (British Medical Association, 2009). So, if capacity is being assessed in relation to the making of a will,

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for example, the assessor should be aware of the extent of the person's property and the identity of those who may have claims on the estate, such as a spouse or family members (for further details on testamentary capacity, see Chapter 58). In terms of medical treatment, relevant information would include specific information about what is involved in the proposed course of treatment, why the treatment is necessary, any options or alternatives to the treatment, and the reasonably foreseeable consequences of consenting to or refusing treatment, or indeed failing to decide—i.e. the risks and benefits (MCA *Code of Practice*, Chapter 3).

The required level of understanding must not be set too high; the person concerned need not understand every detail of what is being explained, just the salient factors. What is clear is that the person concerned must be given something to weigh and assess, such as detailed options; it is not appropriate to start an assessment with a 'blank canvas' (*CC v KK and STCC* (2012)).

Given that 'the more information that the participant must understand, and the more complex the nature of that information, the more impact it will have on an individual's capacity to understand' (Gunn et al., 1999, p. 278) the type of information and the way in which it is presented is of the utmost importance. In cases of borderline capacity, this may well tip the balance in favour of a finding of capacity. In *Heart of England v JB*, Peter Jackson J summarized the approach to be taken:

[w]hat is required here is a broad, general understanding of the kind that is expected from the population at large. JB is not required to understand every last piece of information about her situation and her options: even her doctors would not make that claim. It must also be remembered that common strategies for dealing with unpalatable dilemmas—for example indecision, avoidance or vacillation—are not to be confused with incapacity. We should not ask more of people whose capacity is questioned than of those whose capacity is undoubted. [para. 26]

Clear communication is necessary even when certain outcomes make for uncomfortable conversations; the use of euphemism should be avoided (Emmett et al., 2013). This underscores the supported decision-making principle of s1(3) discussed earlier.

Retaining information

Capacity is assessed at the 'material time', that is at the time the decision needs to be made and the assessment carried out. The fact that an older person with memory deficits can only retain the information for a limited period does not prevent the person having capacity as long as information is retained for as long as is needed to make the decision (s3(3)). If an older person suffers from dementia, it is irrelevant that the information is lost and forgotten after this relevant period has passed. Aids to assist a person to recall information might need to be considered, such as

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pictures or photographs, in line with the supported decision-making principle of the Act.

Using and weighing relevant information

One of the trickiest aspects of the MCA capacity test is judging a person's inability to 'use and weigh' relevant information as part of the process of making the decision. The ability to use and weigh information is often affected by psychiatric disorders, psychoses, delusions, and affective states (Hotopf, 2013).

The courts have interpreted the using and weighing requirement as testing whether a person can 'engage in the decision-making process itself and . . . be able to see the various parts of the argument and to relate the one to another.' (*PCT v P, AH and the Local Authority* (2009), para. 35). In the United States, the capacities for *reasoning and deliberation* have been said to require:

... capacities to draw inferences about the consequences of making a certain choice and to compare alternative outcomes based on how they further one's good or promote one's ends. Some capacity to employ at least very rudimentary probabilistic reasoning about uncertain outcomes will commonly be necessary, as well as the capacity to give due consideration to potential future outcomes in a present decision. Reasoning and deliberation obviously make use of both capacities mentioned earlier: understanding the information and applying the decision-maker's values (Buchanan and Brock, 1990, p. 25).

As before, it is important to remember that not all the details of a proposed act or decision need to be weighed and used, just the salient details. Also, because a person makes a perceived unwise decision this does not necessarily mean that she is unable to use and weigh relevant information.

Case Study 3

Miss Jackson is an intelligent, unmarried, retired solicitor, who lives alone. She has a history of bipolar affective disorder. She seems to be a little high in her mood. She continues to take her medication and she manages her day-to-day affairs without any obvious difficulties. Her nephew, also a lawyer, is concerned that she is giving excessively large sums of money to the local charity for homeless people. He thinks she may not have the capacity to make such decisions because her reasoning has been affected by her mania. He wants to approach the Court of Protection to argue that she lacks the capacity to run her financial affairs. She disputes this

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vigorously and points out that she has always given money to local charities.

If we believe Miss Jackson is simply being unwise, we cannot on that ground alone say that she lacks capacity. She must be allowed to make unwise decisions. But if we believe that her decision to spend her money this way is made because she is unable to weigh and use information owing to her disorder, then we should decide she lacks capacity and take steps to make sure that decisions are made in her best interests, which may or may not include giving money to this particular charity. In this case, the amounts of money given to the charity may assist the determination of capacity. Are the sums broadly the same as given previously, or are they significantly inflated above what she would usually consider giving?

But, more importantly, what is the rationale for her donations? Does she understand the sums involved, how much money she has at her disposal, and the consequences of her actions? In other words, is she able to weigh the advantages and disadvantages of her actions?

Of course, the difference between being unwise and being unable, due to mental disorder, to weigh up matters appropriately in order to make a decision, which would constitute a lack of capacity, is sometimes going to be a fine distinction to draw. There is also a certain amount of flexibility in this provision. Some of the more controversial findings of incapacity made by the courts in the past have been as a result of applying this rather amorphous standard (Bartlett, 2005, para. 2.24). Some commentators have questioned whether it makes sense to argue that a wholly unwise decision could yet be capacitous (Culver and Gert, 2004). But this is to suggest that an outcomes-based assessment of capacity (as mentioned earlier), rather than a functional one, should be preferred. This is a point of view that might seem to have some initial validity, except that it impedes the person's ability (and right) to make autonomous decisions. It tends to position the individual's choices as vulnerable to outside interference. If the world thinks that Miss Jackson is being unwise, on this view, she can be declared to lack capacity, even if she can give adequate reasons for her choices. This runs counter to the position adopted by the MCA, which allows that we can be eccentric without thereby lacking capacity.

Communicating the decision

Some people with physical disorders of the brain following head injury or stroke, for example, might be unable to communicate a decision, and so may be unable to satisfy this part of the functional test. A small minority of people may also have what is termed 'locked-in syndrome', so while being able to understand, retain, and weigh information, they may not have the ability to communicate a choice. Remembering that all practicable steps should be taken to assist a person to demonstrate

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capacity, it is particularly important to consider (and record) any tools, specialists, or carers who could be brought in to aid communication. Any residual ability to communicate, such as blinking an eye to indicate 'yes' and 'no', would be enough to exclude a person from this category (Explanatory Memorandum to the MCA, para. 27).

Unwise decisions

As we touched on earlier, unwise decisions do not alone lead to a finding of incapacity. This is made explicit at s1(4) of the MCA: 'A person is not to be treated as unable to make a decision merely because he makes an unwise decision.'

As we know, human beings are not wholly rational and are prone to make unwise decisions. However, separating unwise decisions from incapacitated ones and allowing people to make choices that might be considered manifestly unwise can be particularly challenging for professionals who have been 'trained to a protective instinct' (Hedley, 2014). Research suggests that assessors will often struggle to reconcile the need to respect an older person's autonomy with their perceived duty to keep that person safe (Emmett et al., 2013; Williams et al., 2012; Series, 2015). As a result, it is not altogether surprising that people who make what are perceived to be foolish decisions are more likely to be found to lack capacity than those who agree with the decision maker—especially when the decision impacts on the person's health and welfare in some serious way (House of Lords, 2014). Nonetheless, the courts have repeatedly cautioned against what judges have termed the 'protective imperative' in case law. Turning again to *Heart of England v JB* (2014), Peter Jackson J noted:

The temptation to base a judgement of a person's capacity upon whether they seem to have made a good or bad decision, and in particular upon whether they have accepted or rejected medical advice, is absolutely to be avoided. That would be to put the cart before the horse or, expressed another way, to allow the tail of welfare to wag the dog of capacity. Any tendency in this direction risks infringing the rights of that group of persons who, though vulnerable, are capable of making their own decisions. Many who suffer from mental illness are well able to make decisions about their medical treatment, and it is important not to make unjustified assumptions to the contrary. [para 7]

Case Study 4

Mr Siddique was admitted to an acute medical ward with a delirium caused by a urinary tract infection. When he recovered it was found that he still had cognitive impairment and his niece, his closest relative, confirmed that he had been forgetful for over a year. He

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said that he wished to return to his home, but he was disoriented on the ward, and an occupational therapy assessment at his home showed that it was squalid and that he had sequencing problems when asked to make a pot of tea. The multidisciplinary team felt that he would be much better off in long-term care.

In order to take things forward, there must be an assessment of Mr Siddique's capacity to make a decision about his place of residence. An outcomes-based approach might be inclined to the judgement that his wish to go home, despite the problems, is itself a sign that he lacks the capacity to make this decision given the potential risks. This would, however, be problematic because it suggests that our ability to make a decision depends on us making the right decision. The question that is then begged is: who decides what is right? The reason this approach is regarded as wrong is because it rules out from the beginning the possibility that the person concerned should be the one who determines what is right.

If Mr Siddique says that he wishes to go into a care home, it may well be said that he makes this decision with capacity (because he is clearly able to weigh up the retained information, which he understands, and he is able to communicate his decision). Conversely, if Mr Siddique says he wishes to go home, the judgement may well be that he lacks capacity (because he is not weighing up the relevant information in the right way). However benign, the outcomes-based approach is inevitably paternalistic: in laying great store by the need to do good and avoid harm it completely ignores the importance of respecting the person's autonomy. This is a strong temptation to caring professionals who wish to do the best for their patients or clients. It is an interesting phenomenon and takes us back to the point that evaluative judgements and emotions play a role in the assessment of capacity (Greener et al., 2012).

As a practical point, the assessment of residence capacity, which is at issue in the case of Mr Siddique, can seem tricky because the information the person is required to understand, retain, and weigh is not set down and might be debated. But we have suggested that the following would constitute the relevant information:

1. The person should know **why** a change of residence is being proposed: what have the problems been that have caused a concern (e.g. they should know why they had to come into hospital or what has caused a worry in the community).
2. The person should know **what** is being proposed (e.g. they should know that it is being suggested they should move into a care home).
3. The person should be informed if there are **other options** (e.g. that they could go home but extra help is recommended because of the risks identified).

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4. The person should understand the **likely consequences** of making any particular decision, including a decision not to follow the advice being given, as well as the consequences of making no decision at all' (Hughes et al., 2015).

The sliding scale of capacity

One problem that emerges in thinking about capacity concerns whether the threshold of capacity varies depending on the decision that has to be made. In other words, does the more serious the possible consequences of the decision or the more complex the issue which is the subject of that decision mean that a higher threshold of capacity is required? This is sometimes called the concept of 'proportionality' and has received a good deal of judicial support over the years. Typically, the way capacity is assessed in proportional terms will depend on the complexity and gravity of any proposed decision or act. In *Re T* the Court of Appeal determined that although someone might have reduced capacity,

What matters is that the doctors should consider whether at that time he had a capacity which was commensurate with the gravity of the decision which he purported to make. The more serious the decision, the greater the capacity required. If the patient had the requisite capacity, they are bound by his decision. If not, they are free to treat him in what they believe to be his best interests. [para. 28]

Hence, we can think of a sliding scale, where decisions that are riskier require greater demands in relation to the information than decisions that are less risky (Gunn et al., 1999). However, the notion of a varying threshold for capacity is itself controversial (Buchanan, 2004) and on a practical level creates dilemmas for assessors who must decide where a particular capacity threshold lies. Set too high, a person's freedom to make an autonomous decision will not be respected in law; set too low and we run the risk of according respect to a decision that may not represent a person's true autonomous choice if masked by an underlying mental disorder, thereby exposing the vulnerable person to harm and/or exploitation (Richardson, 2013; Law Commission, 2017b).

An alternative approach is to argue that there is simply a threshold of understanding for all decisions (Jonas, 2007; Law Commission, 1995). The upshot of both approaches might be the same if more risky procedures are also more complicated to understand, which will not always be the case! Reflection suggests, however, that there are probably limits to both approaches. Otherwise we might, for instance, have to say that only a very few people would be able to give valid consent to undergo very complicated procedures (neurosurgery say) because only a few would have the requisite capacity based on either the level of risk or the complexity of the information.

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The consequences of incapacity

Where a person lacks the mental capacity to make a particular decision, the decision-maker is faced with a dilemma: in the absence of consent or some other legal justification, any touching of an incapacitated adult may amount to a civil trespass to the person, a criminal assault, or may breach that person's human rights; conversely, failing to carry out a necessary act to protect a vulnerable person's health or wellbeing may expose a decision maker to liability in negligence for breaching the professional's perceived duty of care towards the incapacitated person (*Re F (Mental Patient: Sterilisation)* (1990) per Lord Bridge). In the past, the common law has afforded decision-makers with a defence against legal liability for non-consensual treatment and care through the common law 'doctrine of necessity', provided the proposed act is necessary and in the incapacitated person's *best interests*. This common law defence of necessity is now codified in the MCA at section 5.

The defence against liability under Section 5 MCA

Section 5 MCA allows certain decisions or acts in connection with the care and treatment of incapacitated people to be carried out without consent and without a decision maker incurring criminal or civil liability, if they have a reasonable belief that what is proposed is in the incapacitated person's best interests.

So, before any act is carried out, a decision maker must take reasonable steps to assess capacity under sections 2 and 3 MCA and in accordance with the guiding principles of the Act and *Code* before moving to consider a best-interests decision. What are 'reasonable steps' will depend on the individual circumstances and the urgency of the decision to be made. If a person lacks capacity, but is likely to recover capacity in the future, then if possible, any decision must be postponed until capacity is regained. Equally, we must be satisfied that the person concerned has not made a valid and applicable advance decision refusing the treatment being proposed. If this is the case, the advance decision refusing treatment must be complied with and section 5 would not provide us with protection from liability, even if we thought that treating a person would be in an incapacitated person's 'best interests'.

Section 5 talks about 'a person who does an act in connection with the care and treatment of another' and this wording would also include third parties who are instructed by that person to carry out certain acts. The *Code* suggests that more than one person may be acting in accordance with section 5 at any one time. So donees acting under Lasting Powers of Attorney, Court of Protection Deputies, family members, paid and voluntary carers, and healthcare and social care professionals, may all be involved in the care of the person and may need to make decisions and carry out acts in connection with the person's care and treatment.

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The effect of section 5 is that it places those who make decisions or carry out acts in the reasonable belief that the person concerned lacks capacity, and that what is being proposed is in that person's best interests, in the same position as those who rely on the express consent of adults with capacity as legal authority to act.

Finally, it is important to note that some decisions are excluded from the remit of the Act and the general defence afforded by section 5. These decisions can never be made by a decision maker in an incapacitated person's best interests and can only be taken if the person concerned has capacity and consents to the decision in question. Excluded decisions include consenting on an incapacitated person's behalf to:

- marriage or to a civil partnership
- divorce or dissolution of a civil partnership
- have sexual relationships
- adoption
- voting in an election, and
- fertility treatment.

Section 4—the Best Interest Checklist

An important guiding principle of the MCA (as well as of the Mental Capacity Act in Northern Ireland) is that any act done or decision made for or on behalf of a person who lacks capacity must be done or made in that person's 'best interests'. The only exception is in respect of a valid and applicable advance decision refusing treatment, which must be followed whether or not the refusal is in the best interests of the incapacitated person concerned.

In Scotland, the Scottish Law Commission rejected the notion of best interests standard during the passage of the *Adults with Incapacity (Scotland) Act 2000*, primarily on the grounds that it believed the concept was too vague and did not give due weight to the views of the adult concerned, particularly to their wishes and feelings. Also, given the best interests concept developed in child law it was felt wrong to extend child law concepts to adults with mental disorder (Scottish Law Commission, 1995). Accordingly, the general principles refer instead to the notion of 'benefit':

There shall be no intervention in the affairs of an adult unless the person responsible for authorising or effecting the intervention is satisfied that the intervention will benefit the adult and that such benefit cannot reasonably be achieved without the intervention.
(Part 1, Section 1(2))

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Whether it is 'best interests' or 'benefit', the question arises as to what these terms mean. Our focus here is on the best-interests principle under the MCA.

Determining what is in the incapacitated person's best interests

The *Code* suggests that the term 'best interests' cannot be defined on the grounds that individual cases will always require individual judgements as to what will be best for a particular individual. This can neither be stipulated ahead of time nor in general terms. Instead a checklist of factors is set out at section 4 MCA, to guide decision makers when determining what is best for the person concerned in each specific case. The steps in the list must always be considered (Explanatory notes to MCA, para 28), even if it is simply to acknowledge that a factor may not be relevant and can be disregarded. The section expressly instructs decision makers to consider all relevant circumstances as may be required, so the list is not exhaustive. A summary of the best-interests checklist is set out in Box 52.2.

Box 52.2 Summary of the best-interests checklist at section 4 MCA

Generally

- i Avoid discrimination:** don't decide what is best merely on the basis of a person's age, appearance, condition or behaviour for example.
- ii Consider all relevant circumstances.**

In Particular take the following Steps:

- iii Assess whether the person might regain capacity in near future:** if so, wait until the person can make a capacitous decision.
- iv Encourage participation:** the person concerned must be permitted and encouraged to participate as fully as possible in any act or decision.
- v Avoid being motivated in any way by a desire to bring about the person's death:** when best interests and life sustaining treatment are concerned.

Consider as far as Practicable:

- vi The person's wishes, feelings, beliefs & values:** in particular, any written statements
- vii Take into account views of those caring for him:** or anyone interested in his welfare, if appropriate to do so.

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Source: data from Mental Capacity Act, 2005. © Crown copyright

Each of the points in the checklist in Box 52.2 can be expanded. Here, however, we shall simply highlight particular issues. Some of the points in the checklist are drawn more or less directly from the guiding principles of the Act set out in Box 52.1. For instance, it is part of acting in the person's best interests that he or she should be encouraged to participate as fully as possible in decision-making, which chimes with the supported decision-making principle of s1(3). Similarly, we are enjoined to delay making a best-interests determination if there is the possibility that the person might regain capacity, which echoes the least restrictive intervention principle of s1(6) and the broader enabling spirit of the MCA.

Perhaps a point in the checklist that should be highlighted is the one that states that section 4 is not an exhaustive list and 'all relevant circumstances' must be identified. Arguably, this captures more than any other individual point the thinking behind the concept of 'best interests' being put forward, namely that it must be as broad as the circumstances require. Nothing which might be relevant should be overlooked. Everything should be considered, because almost anything might give an important clue as to what would be best, under these particular circumstances, for this individual person.

In doing so, we might need to consider a wide range of social, ethical, medical, moral, emotional and welfare issues (*Re MM (An Adult)* (2007) at para. 99). Also, we might be required to balance a number of conflicting factors, weighing 'the sum of the certain and possible gains against the sum of the certain and possible losses' in a balance sheet (see Thorpe LJ in *Re A (Male Sterilisation)* (2001) at page 60). Some factors may then need to be ascribed more or less weight, depending on their overall significance in the decision at hand, although the section itself establishes no priority between them. This can lead to practical difficulties associated with s.4 in relation to weighing up the importance of each factor in the checklist, which is a subjective exercise. So, what one carer will think is of great importance (factors which the courts have described as being of 'magnetic importance')³ when determining someone's best interest, another person may not; this in turn leads to different outcomes depending on the professional involved or issues arising between those involved.

An important subjective element must be present in any best-interests determination made. We will return to these criteria in more detail later, but suffice to say that a decision maker should consider, as far as is reasonably ascertainable, the incapacitated person's wishes, feelings, beliefs, and values—both his or her past competent views if known (in particular any written statements), as well as his or her past and current wishes and feelings.

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In addition, reasonable and genuine attempts must be made to consult with those who know the person well. The purpose of this consultation is to find out more information about the incapacitated person, in particular their past and present wishes, feelings, beliefs, and values to help inform the best-interests decision. The consultation process is not to enquire of the consultee what decision should be made. In the Scottish Act, although not using the notion of 'best interests' this is summarized thus:

In determining if an intervention is to be made and, if so, what intervention is to be made, account shall be taken of—

- (a) the present and past wishes and feelings of the adult so far as they can be ascertained by any means of communication, whether human or by mechanical aid (whether of an interpretative nature or otherwise) appropriate to the adult;
- (b) the views of the nearest relative and the primary carer of the adult, in so far as it is reasonable and practicable to do so;
- (c) the views of—
 - (i) any guardian, continuing attorney or welfare attorney of the adult who has powers relating to the proposed intervention; and
 - (ii) any person whom the sheriff has directed to be consulted, in so far as it is reasonable and practicable to do so; and
- (d) the views of any other person appearing to the person responsible for authorizing or effecting the intervention to have an interest in the welfare of the adult or in the proposed intervention, where these views have been made known to the person responsible, in so far as it is reasonable and practicable to do so. (Section 1(4))

The details of individual laws are not something that we can dwell on. We can, however, point to principles. What we see in this statement (as well as in the MCA and the MCANI), is that it is both true that the person in question must remain centre-stage and that the person has to be considered in his or her context: of family, culture, social relationships, history, moral and spiritual beliefs, law, and so on. Our agency, we might say, is situated; which partly means that it involves others (Hughes 2011, pp. 51–3). Hence, we must be interested in what the person thinks now, but also in what he or she might have thought in the past. Similarly, if someone else might be able to tell us what the person once thought, which might be a clue as to what they would now think, we should speak with them.

As with the assessment of capacity, best interests and the availability of treatment must not be determined merely on the basis of a person's appearance, age or behaviour—all relevant factors must be considered. Also, we must not be led by existing prejudices and unjustified assumptions based purely on a person's appearance or diagnosis. This is sometimes called 'the principle of equal consideration'.

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In terms of principles, there are two things to consider: substituted judgements and proxy decision-making. *Substituted judgements* are where someone else is asked to say what they think the person him or herself would have wished or decided under present circumstances, based on past things that he or she might have said or done. A *proxy decision*, alternatively, is where someone is simply asked to express an opinion as to what is best or what should be done. Of course, if asked to act as a proxy, someone may well make a substituted judgement. They may well base their views on things that the person concerned once said or did. But, in a stricter sense, a proxy decision is where the person does not ask ‘What would Dad have wanted under these circumstances?’, but ‘What do I think is best for Dad?’

The worry about proxy decisions is that someone may make a decision for Dad which reflects their own needs—e.g. not to be without a father—but does not express what would be the true wishes of Dad, who said on many occasions that he would not wish to be kept going ‘beyond my sell-by date’. Alternatively, to use a less benign example, we might wish Dad dead because the costs of providing care are eating into our inheritance. For this reason, the MCA’s *Code*, based on the deliberations set out in the earlier review by the Law Commission (Law Commission, 1995), suggests a strong element of substituted judgement: the family member or friend is mainly asked ‘What would she have wanted or said?’ But the fact is that sometimes we simply do not know what the person would have wanted: the particular issue never cropped up in the person’s life and no one can remember any comments directly relevant to it. Luckily, perhaps with this possibility in mind, the *Code* leaves what might be called some wiggle room!

The *Code* suggests, in paragraph 5.53, two aspects that the decision-maker should consider:

- ‘what the people consulted think is in the person’s best interests in this matter, and
- if they can give information on the person’s wishes and feelings, beliefs and values’.

This is significant because it suggests the MCA is concerned both about proxy decisions and about substituted judgements. Whoever is responsible for the decision has to ask about what someone ‘thinks is in the person’s best interests’. This sounds distinct from asking what they think the person him or herself would have thought. In other words, the views of the person concerned who lacks capacity are vitally important, but the views of others are important, too.

The interesting point to note is the suggestion that, even if everyone else agrees on one course of action, if the decision maker feels this is not in the best interests of the person concerned, she must act in accordance with her own judgement of what is best. This tells us that doing what is best for someone must remain a complex personal, social, and moral

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judgement, which is not to be decided by a simple majority vote (Ruck-Keene and Auckland, 2015).

To return to the notion of how we are, inherently, situated in a context of relationships, it makes sense that others can say what would be best simply based on their own judgements. It would seem quite likely, after all (although not necessarily in all cases), that a daughter's sense of what might be best for her father is likely to be close, or as close as we can reasonably presume, to what her father's views might have been. A proxy decision, therefore, in the absence of evidence that might provide a substituted judgement, might actually be a 'proxy substituted judgement'. The direction of this discussion suggests how complicated are the notions of best interests or personal benefit.

In the end, when a person cannot make a decision, someone must decide and judge what is best. These judgements are by no means easy to specify fully. In an interesting clause in the MCA's *Code*, which discusses the possibility of disagreement and the need then to meet with all concerned in order to review the best-interests checklist, it states:

It may be possible to reach an agreement at a meeting to air everyone's concerns. But an agreement in itself might not be in the person's best interests. Ultimate responsibility for working out best interests lies with the decision-maker (*Code* 5.64).

The complexities, we are suggesting, are inevitable because the notions of what might be best or of benefit to a particular person are contingent upon the individual and the circumstances at the time.

Past and present wishes, views, and feelings

The extent to which such past wishes/feelings will influence the outcome of any best-interests determination has been deliberated at some length by the courts. In *Re M* (2009) Mr Justice Munby noted that the weight to be attached to P's [the incapacitated person's] wishes will always be case- and fact-specific:

In some cases, in some situations, they may carry much, even, on occasions, preponderant, weight. In other cases, in other situations, and even where the circumstances may have some superficial similarity, they may carry very little weight. One cannot, as it were, attribute any particular *a priori* weight or importance to P's wishes and feelings; it all depends, it must depend, upon the individual circumstances of the particular case. And even if one is dealing with a particular individual, the weight to be attached to their wishes and feelings must depend upon the particular context; in relation to one topic P's wishes and feelings may carry great weight whilst at the same time carrying much less weight in relation to another topic. Just as the test of incapacity under the 2005 Act is, as under the common law, 'issue specific', so in a similar way the

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weight to be attached to P's wishes and feelings will likewise be issue specific. [para. 35]

In each case, when considering the particular weight to attach to a person's wishes and feelings, the following are important considerations:

- a.** the degree of P's incapacity, for the nearer to the borderline the more weight must in principle be attached to P's wishes and feelings;
- b.** the strength and consistency of the views being expressed by P;
- c.** the possible impact on P of knowledge that her wishes and feelings are not being given effect to;
- d.** the extent to which P's wishes and feelings are, or are not, rational, sensible, responsible, and pragmatically capable of sensible implementation in the particular circumstances; and
- e.** crucially, the extent to which P's wishes and feelings, if given effect to, can properly be accommodated within the court's overall assessment of what is in her best interests (para. 35(iii)).

So best-interests decisions may not always reflect what an incapacitated person wants, but those wishes and feelings will be a significant factor, sometimes *the* most significant factor, in any best-interests determination. Lady Hale confirmed this in the Supreme Court case of *Aintree University Hospital NHS Foundation Trust v James* (2013):

Insofar as it is possible to ascertain the patient's wishes and feelings, his beliefs and values or the things which were important to him, it is those which should be taken into account because they are a component in making the choice which is right for him as an individual human being. [para. 45]

It follows that where a patient's past, present, or future views are ascertainable they represent powerfully important factors in any best-interests decision and very good reasons should exist before deciding to impose treatment on a protesting, albeit incompetent, person (Gostin, 1986). It is also worth noting that the Law Commission, in its report and Draft Mental Capacity (Amendment) Bill, proposed that s.4 should be amended to give 'particular weight' to a person's ascertained wishes and feelings. In doing so, the wishes and feelings of a person would have been given a 'higher status' than all the other factors in s.4 when best-interests decisions were made. The Commission concludes: 'as a general rule, the stronger and clearer the ascertainable wishes and feelings, the greater the weight that should be given to them—due to the greater infringement on the person's autonomy under Article 8(1) of the ECHR if they are not followed.' (Law Commission, 2017b, para. 14.17). However when the Government published its Mental Capacity (Amendment) Bill 2018, which passed into law in May 2019 as the Mental Capacity (Amendment) Act 2019, those recommendations did not find their way into the new legislation.

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Concluding this section, we can say that section 4 of the MCA is all about achieving a decision that is best for the person concerned. Compliance with the Act also provides important protection for decision makers who carry out interventions in the 'reasonable belief' that they are acting in the best interests of the patient. The protection is gained by following the steps set out in the best-interests checklist. Of course, what is necessary to evidence this belief will vary depending on the urgency and gravity of the situation. Nevertheless, if a challenge is subsequently made in the courts and there is a later judicial finding that the act is not in the person's best interests, protection will be given so long as the decision maker had a 'reasonable belief' that it was, and has objectively evidenced that he has followed the statutory steps. This highlights again the importance of detailed record keeping, as thorough and well-documented notes will evidence that the decision maker has acted lawfully if faced with any future legal challenge.

Limitations on Section 5 Acts: Restraint and deprivation of liberty

Occasionally, older people with declining cognition may behave in ways that pose risks to themselves or to others, so that restraint or force is required to administer treatment and care in their best interests. One of the most common reasons for older people with dementia to move into care is to manage risk when their behaviour might endanger them or be threatening to others (Jackman, 2014).

If we do an act that is intended to restrain the incapacitated older person, the protection under section 5 will only apply if the person doing the restraining reasonably believes it is necessary to prevent harm to the incapacitated person in their care, and the restraint is proportionate to the likelihood and seriousness of harm (i.e. the benefits of the treatment outweigh the harm caused by the restraint) (s6(2) and (3) MCA). Section 6 must be read in the light of the overriding principles (Box 52.1).

Principle 1(6) is relevant:

Before an act is done, or decision made, regard must be had to whether the purpose for which it is needed can be effectively achieved in a way that is less restrictive of the person's rights and freedom of action.

Accordingly, restraint must be in a person's best interests and other less restrictive options such as persuasion and discussion should have been explored first, before any restraint is used. This principle brings us back to the fundamental point of capacity legislation: one of its main aims is to protect the rights of people with impaired decision-making abilities. The aim is to promote their rights to participate in decisions made about them; and if others make decisions about them they should nevertheless be respected as individuals. A basic ingredient of this respect is that they should be allowed the freedom to do what they can with as much liberty as possible under the circumstances that apply to them.

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The effect of these limitations is that the s.5 defence can only be relied on when restraint amounts to a *restriction* of liberty and only if the necessary conditions of s.6 are met (which should be documented) and it is in P's best interests.

If the circumstances surrounding the administration of treatment and care move beyond mere restraint to a *deprivation of liberty* (such as confining a person and repeatedly needing to restrain a person to administer treatment or care, or medicating an individual for prolonged periods in a person's best interests as part of a treatment plan), then it is not permitted by s.5, and alternative legal authority must be sought either from the Deprivation of Liberty Safeguards of the MCA, (which are shortly to be replaced by the new Liberty Protection Safeguards via the Mental Capacity (Amendment) Act 2019), via the Court of Protection, or using the Mental Health Act 1983 where appropriate.

Article 5 of the European Convention on Human Rights protects a person's right to liberty and security against arbitrary interference by the state (including state actors—such as NHS and local authority employees, police, judges, and so on). A person's right to liberty can only be interfered with lawfully in certain defined situations, one of those being where a person is 'of unsound mind', but only then when such interference is 'in accordance with a procedure prescribed by law' and when the detention can be reviewed quickly so that it can end when it is no longer justified.

Identifying when a deprivation of liberty (DoL) arises is, therefore, important, because depriving someone of his or her liberty without lawful authority, and without proper procedural safeguards, would potentially breach Article 5—which is what happened to the UK Government in the case of *HL v UK* (2005). Prior to this, a large number of disabled people in the UK, many of whom were older people with dementia, were being confined in long-stay hospitals and nursing homes without the capacity to consent to their living arrangements and without any proper procedural safeguards against arbitrary detention. The Deprivation of Liberty Safeguards (DoLS) under the MCA were subsequently introduced to address this gap.

Of course, this still left the thorny issue of what a deprivation of liberty looks like. The Supreme Court ruling in *P v Cheshire West and others* (2014) offers the most authoritative domestic guidance on what may amount to a DoL in health and social care settings.

The Court stated that we should look first at the concrete situation of the person concerned, looking at 'the type, duration, effects and manner of implementation of the measures in question' (*Guzzardi v Italy* (1980) (at para. 92)). Moreover, the difference between restriction and deprivation is 'one of degree and intensity, and not one of nature or substance' (para. 93).

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Where the person lacks the capacity to consent to their care and treatment arrangements, the 'acid test' would then fall to two central elements: whether the incapacitated person concerned

1. is under 'continuous supervision and control' and
2. is 'not free to leave'

Case Study 5

Mrs L is 93 and has severe Alzheimer's dementia. She lives alone in the upper floor flat of a 2-storey building. There is a fence and two gates enclosing the garden to prevent her from wandering. She has access to her garden via a door which is locked with a yale lock and which Mrs L can operate to access the garden when she wishes. Door sensors switch themselves on in the evening and off in the morning and would be activated if Mrs L were to leave the property at night. An alarm call would automatically be made to one of her daughters nearby and, if not available, would re-route to the emergency services. This would enable Mrs L to be guided safely back home, but has not been triggered since they were installed. She is provided with a package of care by the Local Authority, which consists of three visits a day by specialist dementia carers.

These facts are taken from *W City Council v Mrs L* (2015), a reported decision of some interest as it is a rare example of where a person is considered not 'free to leave', but is otherwise not 'under continuous supervision and control'. On the facts, although Mrs L would have been returned home had she attempted to leave, and there were measures in place to ensure this happened, she was, nevertheless, found to have 'ample time to spend as she wished in her own home, and the carer's visits were the minimum necessary for her safety and wellbeing, being largely concerned to ensure that she is eating, taking liquids and coping generally in other respects'. Accordingly, she was not under continuous supervision and control in her own home, and despite being not free to leave her house she was found not to be deprived of her liberty.

The case also raises the important point that a DoL can potentially arise in the privacy of a person's own home. For Article 5 to be engaged, any DoL must be 'imputable to the state', meaning it is one for which the state can be said to be responsible. This can arise, and usually does arise, when a public authority is directly responsible for the care and treatment of the incapacitated person in a state-run nursing home or hospital for example. Nonetheless, it is easy to imagine that a person could be deprived of her liberty in a private nursing home, or hospital—or indeed her own home (or other private living arrangement)—which is exactly what was being argued by the local authority in Mrs L's case. In such

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situations, the state may still have a positive obligation to provide effective protection of an individual, where it:

knows or ought to know that a vulnerable ... adult is subject to restrictions on their liberty by a private individual that arguably give rise to a deprivation of liberty (*Re A and Re C* (2010) at para. 95).

This would then lead to a duty on the part of the state authority to investigate the DoL and 'a positive obligation, both under Article 5 alone and taken together with Article 14, to take reasonable and proportionate measures to bring that state of affairs to an end, involving the court if necessary' (para. 95). Although these issues were not argued fully in Mrs L's case, the case illustrates the potential positive obligations the state can have to protect vulnerable people from deprivations of liberty, even where it has only a partial or indirect involvement in that person's care arrangements (Law Society, 2015 at para. 2.50).

Life and death issues

The observant reader will have noticed that we did not deal with the item in the best interests checklist (Box 52.2), which states that those providing care should avoid being motivated in any way by a desire to bring about the person's death. This seems worthy of consideration separately because many difficult decisions will need to be made in connection with dying patients.

Rightly or wrongly, when the MCA was being passed into law there was a concern that it would allow euthanasia or physician-assisted suicide 'by the back door'. In UK law there is a distinction made between, on the one hand, unlawfully cutting off life deliberately by administering, say, a lethal injection of drugs which ends life prematurely and, on the other hand, withdrawing treatment in a dying patient's best interests so nature can take its course. Given the concerns expressed at the time of the MCA around the risk of euthanasia however, a number of clauses were inserted that aim to close down such a possibility (e.g. sections 26(5a) or 62).

In any case, medical care and treatment should, on the whole, be aimed at maintaining life (*Airedale NHS Trust v Bland* (1993)). But the issues need to be measured carefully.

In 2013 the Supreme Court case of *Aintree v James*, Mr James had acquired an infection in hospital in May 2012, which led to him being admitted to the critical care unit where his condition rapidly deteriorated and he suffered multiple organ failure. Some four months later, the hospital applied to the Court of Protection for a number of declarations, including that it would be in Mr James's best interests not to receive certain treatments, including CPR, in the event of further deterioration. The family, conscious that, in spite of his condition, Mr James appeared still to enjoy his life, contested the application. They were successful at the first hearing in the Court of Protection. By the time the case came on

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appeal to the Court of Appeal, Mr James's condition had significantly deteriorated to the point that he was largely comatose and ventilator-dependent. The Court of Appeal allowed the Trust's appeal and granted the declarations sought. On 31 December 2012, Mr James suffered a cardiac arrest and died, although his widow was allowed to appeal his case to the Supreme Court. Lady Hale (with whom the other Justices agreed) delivered the lead judgment. In doing so she clarified a number of established principles relevant to medical treatment and end-of life-decisions.

1. The starting point is a strong presumption that it is in a person's best interests to stay alive. The *MCA Code* acknowledges this: 'All reasonable steps which are in the person's best interests should be taken to prolong their life' (*Code* para. 5.31). But this presumption is not absolute.

2. There will be a limited number of cases where treatment is futile, overly burdensome to the patient, or where there is no prospect of recovery. Where the patient is close to death, the object may properly be to make his dying as comfortable and as dignified as possible, rather than to take invasive steps to prolong his life for a short while. The decision maker must make a decision based on the best interests of the person who lacks capacity and must not be motivated by a desire to bring about the person's death for whatever reason, even if this is from a sense of compassion. Healthcare and social care staff should also refer to relevant professional guidance when making decisions regarding life-sustaining treatment (*Code* para. 5.31), which would in the UK include relevant guidance from the General Medical Council (General Medical Council, 2010; para. 16, pp. 16–19).

3. Futility should not be confined to questions of whether treatment could cure or at least palliate the life-threatening disease or illness; futility should be considered in a broader sense, recognizing that a treatment may bring some benefit to the patient (and so not be futile) even though it has no effect upon the underlying disease or disability. Furthermore 'recovery' does not mean a return to full health, but the resumption of a quality of life which the patient would regard as worthwhile.

4. In circumstances such as these (where treatment is considered futile, overly burdensome, and where there is no prospect of recovery), it may be that an assessment of best interests leads to the conclusion that it would be in the best interests of the patient to withdraw or withhold life-sustaining treatment, even if this may result in the person's death.

5. At the end of life, the question to be asked is whether it is lawful and in the best interests of a patient for treatment to continue, not whether it is in a person's best interests for treatment to be withdrawn and the patient allowed to die. The legal question to be determined is whether doctors have the 'right to continue lawfully to

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invade the bodily integrity of a patient without his consent' (*Airedale NHS Trust v Bland* (1993)).

6. Furthermore, patients (and their families) cannot demand that a doctor administers treatment which a doctor believes is not clinically indicated, although patients with capacity can refuse such treatment (*R (Burke) v General Medical Council* (2005) at para. 50).

The point that an adult with capacity can refuse treatment, even if that refusal would bring about the person's death, was of course established well before the *Aintree* judgment in cases such as *Re B (Consent to Treatment: Capacity)* (2002) where Dame Elizabeth Butler-Sloss stated that a competent patient has: 'an absolute right to refuse to consent to medical treatment for any reason, rational or irrational, or for no reason at all, even when that decision may lead to his or her death'. The case found that doctors had trespassed in providing mechanical ventilation to Ms B, who was paralysed from the neck down following a haemorrhage, when it was her competently made request not to be treated. Dame Butler-Sloss went on to say:

There is a serious danger, exemplified in this case, of a benevolent paternalism which does not embrace recognition of the personal autonomy of the severely disabled patient' (*ibid.*).

It is worth commenting that the circumstances envisaged where it would be permissible not to try to prolong someone's life are those that would be sanctioned by the well-known doctrine of ordinary and extraordinary means. This states that there is a moral obligation to pursue ordinary means, but not extraordinary, where 'extraordinary' is understood to mean those treatments (or investigations) that would be ineffective or burdensome. The law reflects this type of thinking.

Support for decision-making

Various legal mechanisms have been developed over the years to enable those with compromised capacity, or worried by the prospect of losing capacity, to make arrangements in case they should become fully incapacitated. For instance, the MCA amended the previous arrangements for Enduring Powers of Attorney (EPAs) and substituted Lasting Powers of Attorney (LPAs). Whereas EPAs covered only property and financial matters, LPAs come in two forms: they cover property and affairs, like the EPA; and personal welfare, which includes decisions about health and where the person should live. A personal welfare LPA can only be used if the person lacks the ability to make decisions for him or herself; whereas the property and affairs LPA can come into effect at any time. There are two points to note.

First, in the move from the EPA to the LPA we see an enlargement of the field in which the law accepts that we may wish to have the protection of someone of our own choosing making important decisions for us. Whilst the details will be different in other jurisdictions, the inclination to

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preserve autonomous decision-making is a strong one in liberal democracies. Second, the law in this regard is acknowledging the importance of proxy decision-making. Under the MCA, however, the attorney appointed by the LPA must act in the person's best interests, so that all of the points made here apply. The attorney, therefore, shoulders a significant burden in terms of protecting the individual's human rights.

What if there is no one to represent the views of the individual who lacks capacity? One of the important safeguards brought in by the MCA is the Independent Mental Capacity Advocate (IMCA). In the MCA's *Code* it states that the IMCA service provides safeguards to those who

- lack capacity to make a specified decision at the time it needs to be made
- are facing a decision on a long-term move or about serious medical treatment and
- have nobody else who is willing and able to represent them or be consulted in the process of working out their best interests (para. 10.1).

In common parlance, it is said that those who are 'unbefriended'—those patients with no relative or carer—require an IMCA at times when critical decisions are being made about health or care, which includes decisions about place of residence. There are cases, for example, where there might be abuse, where an IMCA can be appointed even if family are involved. In addition, the DoL legislation stipulates that an IMCA should be involved where there might be a DoL. Unfortunately, there are still wide disparities in access to IMCAs, which the Department of Health is seeking to ameliorate. Again, the details do not need to detain us. But the principle—that vulnerable people who lack capacity should be 'supported and represented' when they are faced with significant decisions—is surely beyond dispute. Where there is good practice, of course, the person will be supported and represented by those who provide normal care. But the tendency to creeping paternalism, an outcomes-based approach to capacity assessments for instance, albeit benignly inspired, is too prevalent to do away with independent safeguards. If anything, it seems likely that such safeguards should be extended in the future.

Even before the MCA came into force, case law (e.g. *Re T*) had established the legal force of advance decisions. The MCA establishes in statute law that a patient may refuse certain sorts of treatment in the event that he or she loses capacity in the future. Advance decisions must be made when a person is deemed to be capacitated, cannot request anything that is against the law (such as assisted suicide), and must set out exactly which treatments should not be given, and the circumstances under which the refusal would be honoured. The key words are that the advance refusal of treatment must be 'valid' and 'applicable'. Its validity depends on its form and, where it concerns refusal of life-sustaining treatments, it must be in writing, signed, and witnessed, and state clearly

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that the decision applies even if life is at risk. Some treatments cannot be refused in advance, especially those for mental illness administered under the Mental Health Act, which, with the exception of ECT, can be given without consent in certain circumstances (see Chapter 58).

More problematic, perhaps, is the notion of ‘applicability’, which suggests that if there has been anything that might not have been anticipated when the advance refusal was made, or if the circumstances were not quite those that now obtain, then the advance refusal of treatment need not be followed. This obviously makes some sense. But it also undermines the surety of the advance directive and places in jeopardy the autonomy it is meant to protect.

In their report on dementia, the Nuffield Council on Bioethics acknowledged the importance of protecting the person’s right to determine what happens to them:

If we are to promote people’s interests in their own autonomy and well-being, and in particular in their *own* notion of what constitutes their own well-being, then it is right that the law should, as at present, permit those who feel so strongly to make those wishes effective (Nuffield Council on Bioethics, 2009, para. 5.40).

However, the report also cautioned that ‘an advance refusal of treatment may not operate in the way that the person in fact envisaged’ (Nuffield Council on Bioethics, 2009, para. 5.41). Hence, the report commended the broader notion of advance care planning, which can take various forms, but which might involve LPAs or advance statements in which the person expresses his or her preferences on a variety of issues. Even if these preferences do not have to be honoured, once established they feed into any judgements about the person’s best interests and cannot simply be ignored.

United Nations Convention on the Rights of Persons with Disabilities

We began this chapter with the notion that mental capacity exists as a threshold concept in law: only decisions made with capacity are regarded as autonomous and therefore worthy of respect; choices made by those who lack capacity can be overridden by others acting in their perceived ‘best interests’ or benefit. However, as we have seen, incapacity is no longer viewed as ‘an ‘off-switch’ for an incapacitated person’s rights and freedoms’ (*Wye Valley NHS Trust v B* (2015), para. 11). Over the past twenty years, the impact of international human rights instruments, most notably the European Convention on Human Rights, as well as broad legislative reform of incapacity laws in the UK, has prompted greater recognition of the rights of the incapacitated adult and a more patient-centred approach to decision-making. So, while this binary ‘capacity/incapacity’ distinction still persists in law, with different legal consequences flowing from each outcome, the idea that incapacity leads

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to a complete abrogation of the legal rights of the individual is increasingly difficult to justify (Donnelly, 2014).

The United Nations Convention on the Rights of Persons with Disabilities (CRPD) (United Nations, 2006), in particular, which the UK Government ratified in 2009, challenges established notions of capacity and its legal consequences. The CRPD prohibits discrimination against people with disabilities and promotes the enjoyment of fundamental rights for people with disabilities *on an equal basis with others*. Its purpose is to promote, protect, and ensure the full and equal enjoyment of all human rights and fundamental freedoms by all persons with disabilities, and to promote respect for their inherent dignity.

As a theoretical underpinning, the CRPD poses difficult questions for the MCA and its mental capacity/best-interests model of decision-making. Article 12, in particular, provides that state parties shall recognize that persons with physical and mental disabilities enjoy ‘full legal rights and equal recognition before the law’ (Article 12(1)) and ‘enjoy legal capacity on an equal basis with others in all aspects of life (Article 12(2)).’

The Convention causes us to question whether the functional test of capacity under the MCA, based as it is on a mental disorder, is discriminatory and contravenes Article 12 given that, via the diagnostic test, it is solely applied to people with disabilities. It also causes us to be concerned about the best interests ‘substitute’ decision-making model of the MCA, given this has the potential to deny incapacitated people their ‘will and preferences’ and legal capacity before the law.

Moreover, although the MCA’s presumption of capacity, support for decision-making, respect for the wishes, feelings, and values of the incapacitated individual in the best-interests standard go some way toward achieving the rights conferred by the CRPD, these principles do not go far enough (Donnelly, 2016). Despite the enabling rhetoric that accompanies the MCA, the lack of procedural oversight and safeguards in the Act suggests that it falls short of compliance with the CRPD. Often the reality of clinical decision-making is that ‘the prevailing cultures of paternalism (in health) and risk aversion (in social care) have prevented the Act from being widely known or embedded’ in practice (House of Lords, 2014).

Although the CRPD is not yet incorporated into UK domestic law (in the same way the rights and freedoms guaranteed by the European Convention on Human Rights are enforceable in domestic courts via the operation of the Human Rights Act 1998), we should nevertheless take it seriously. The Convention’s explicit social development dimension is steering the direction of mental health and capacity laws and influencing reform, not just in the UK (Law Commission 2017a,b), but in other jurisdictions worldwide.

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Storck v Germany [2006] 43 EHRR 6

W City Council v L [2015] EWCOP 20

Wye Valley NHS Trust v B [2015] EWCOP 60

Notes:

1 Mrs Murray (as is true of all the vignettes we use) is fictitious, but the wish to die on her own floor rather than in a care home was expressed by KK in the case *Re KK; CC v KK and STCC* [2012] EWHC 2136 (COP), [2012] MHLO 89. She said: 'If I die on the floor, I die on the floor. I'd rather die in my own bungalow, I really would'. The judge did not consider that this meant she lacked capacity, but rather said: 'it is an example of how different individuals may give different weight to different factors'.

2 McFarlane LJ' stands for 'Lord Justice McFarlane'; later we shall refer to 'Peter Jackson J' which stands for 'Justice Peter Jackson'; and so on.

3 Although the MCA lays down no formal ranking or hierarchy between the various factors to be considered in section 4, the courts have repeatedly endorsed the notion that one or more factors may have overwhelming or 'magnetic importance' in influencing or even determining an outcome (see *ITW v Z* (2009) EWHC 2525 (Fam) at para. 32; *KGS v JDS* [2012] EWHC 302 at para. 23; and *PB v RB & Anor* [2016] EWHC COP 12 at para. 29).



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Ethics of living and dying with dementia

Chapter: Ethics of living and dying with dementia

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Introduction

The occurrence of memory problems is traditionally the most prominent cognitive symptom of dementia, and the illness has, for a long time, been approached as a memory disorder. However, the core of the disorder and the reason why it scares so many does not lie in the reduction of memory function, but rather in the meaning touched upon in the etymology of the word 'de-mentia', which refers to losing one's mind. And since the mind is traditionally viewed as the seat of our identity, dementia is first and foremost feared as a loss of 'self', and consequently of 'self-determination'. People affected by the disorder gradually lose a grip on their own internal processes and control of their own lives. This is linked with a loss of all learnt skills and an increasing and ultimately total dependence on others. Therefore, the last phase often requires admission to a nursing home.

Ethics of living and dying with dementia

We can therefore describe the points of departure for a 'good' (in the moral sense) care policy for dementia on the basis of these summary characteristics:

- The gradual, progressive nature of the illness means that a person with dementia remains actively involved in his or her situation until quite a long way into the disease process, despite cognitive impairment; the person will also actively attempt to adapt to the consequences of the disease, including, for instance, adjusting expectations and a changed outlook on quality of life, as is also observed in other chronic disorders. Offering support in this adaptation process is, therefore, of great importance, requiring adjustment and specification of the ethical principle of 'respect for autonomy'. This 'respect' demands that care staff actively engage in connecting with the perspectives and the current perceptions of people with dementia. A dilemma that may arise here is that the person with dementia may express desires and wishes in the present that are at odds with earlier views communicated about living with dementia—for instance, views that may have been expressed in a written advance directive (AD) prior to dementia arising.
- Dementia, nevertheless, does result in an increasing loss of competence. This means that progressively more decisions (varying from financial matters to treatment decisions and ultimately decisions pertaining to the daily care structure) have to be taken on by others. A good balance between supporting residual opportunities for self-determination and—where this is no longer possible—ensuring proper representation is, therefore, of great importance in all phases of dementia.
- Dementia is an incurable disease with few treatment options. Currently, there is little that can be done other than alleviating symptoms, and perhaps slightly curbing, or delaying, progression. However, what many physicians (and next-of-kin!) do not fully realize is that dementia is also a terminal illness that results in a significant reduction in life expectancy. This prognostic fact justifies an approach towards care policy based on the principles and aims of palliative care.

A number of ethical questions about the care provided to people with dementia are addressed in further detail in the following discussion in light of the three principles for good care outlined here. The meaning of (respect for) autonomy as an ethical principle, the complex ethical issues surrounding the concept of competence, and the position of next-of-kin and proxy decision makers (simply referred to here as representatives) is successively discussed. The role of written ADs in organizing care for people with dementia is also addressed in this context. Central to our argument in dealing with ADs, in supporting autonomy, in anticipating the future, and in providing tailored end-of-life care is the concept and practice of advance care planning (ACP). The chapter concludes with a discussion of a number of ethical questions concerning the end of life.

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Respect for autonomy

The principle of 'respect for autonomy' may be viewed as an inalienable attainment in modern ethics. This status is attributable to the process of democratization and patient emancipation, which has completely changed the delivery of healthcare since the 1970s and has resulted in a shift in healthcare ethics from medical paternalism to a strong emphasis on patient rights. The most important result of respect for autonomy within medical ethics is the principle of 'informed consent'. Informed consent means that medical treatment cannot, in principle, be permitted without prior permission from the person concerned based on information appropriate to the issue at hand provided by healthcare professionals (Tauber, 2005).

Notwithstanding the achievements of modern healthcare ethics, there is also criticism because of its rather reductionist approach, focusing predominantly on individual autonomy and presupposing an ideal of self-determination, which tends to underestimate the relevance of human relationships as well as in understanding autonomy. From the fields of geriatric ethics and the ethics of care, calls have been made for a more nuanced approach (Spielman, 1986; Walker, 1998; Agich, 2003; Tauber, 2005).

In this connection, it is first of all relevant to underline that 'showing respect' comprises more than just information provision to allow an independent choice. From an ethics of care perspective, attention is called for the layered structure of the concept of 'autonomy', from which at least two meanings may be distinguished (Agich, 2003). These should be viewed as two related, but nevertheless distinct, ethical dispositions. The first may be described as a defensive position—expressed in the desire to be safeguarded against intervention by others. This is also referred to as the principle of 'non-interference'. The second may be expressed as an affirmative position and translates, as it were, into the desire to live life in one's own way and according to one's own standards. From the standpoint of the prevalent rights-based ethics, as well as in the statutory regulations regarding informed consent, the emphasis lies on the former meaning of autonomy, and the provision of appropriate information by healthcare staff is considered sufficient to satisfy the second condition. However, in ethical terms, this is a rather narrow interpretation of the respect for autonomy concept that rests on an understanding of ourselves as, in essence, independent and self-sufficient individuals. Furthermore, it is an interpretation that does not always agree with what people expect from physicians attending them when it comes to health care decision-making. After all, apart from information, people also want advice. Sometimes they require some discussion about the decision to be taken and often need active support, particularly where there is a lot at stake. 'Respect' for autonomy, therefore, does not legitimize a noncommittal approach, but rather demands that healthcare staff actively assist health service users in taking those decisions that they can identify with in such a way that these become their 'own'

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choices. That is more than simply honouring people's rights and wishes. Especially in care and treatment relationships, the relevance of the second meaning of the autonomy concept becomes clear. After all, autonomy as 'living according to one's own standards' does not mean that people lead their lives by fixed standards, isolated from the world and its uncertainties. On the contrary: autonomy in this sense is a contextual and dynamic concept that reflects a human need and tendency to identify oneself with changing life circumstances, such as illness and other (major) life events (Agich, 2003).

The relevance of this layered structure of the concept of respect for autonomy is evident where this involves caring for people with cognitive impairments, as is the case for (various forms of) dementia. Here, an active approach by healthcare staff, when taking care and treatment decisions, is indispensable from the outset. In this context, good care includes the ability to tailor information carefully to the level of comprehension of the person with dementia, to take into account the speed at which that person thinks and works, to encourage them—where necessary—to be assisted by people they trust, as well as a willingness to offer—or to actively encourage—follow-up discussions in order to provide an opportunity to carefully think the issues through. In any case, health professionals should not rush into assuming that a person with dementia is incompetent (or no longer competent) to make the necessary decisions, and take refuge in consulting with their family or representative. In the past, this was often the indirect route by which the care and treatment of people with dementia was decided, but this is no longer an acceptable approach these days: patient emancipation, which in the past contributed to people with physical illnesses being considered as full participants in discussions with healthcare staff, has now also reached that group of people with dementia. This is primarily the result of a growing interest in the patient perspective: 'a shift away from pathology to people' (Nolan et al., 2002).

Under the dominance of the biomedical paradigm, it was for a long time assumed that people with dementia had no awareness of their condition, whereas we now know that people with dementia are certainly aware of what has befallen them and they try as hard as they can to adapt to the consequences of what is going on in their mind. However, without help and assistance from their environment they will not succeed in doing so, which is why Tom Kitwood (1998)—one of the first advocates of the so-called person-centred care—made a powerful plea for communicative and interactional ethics, and pointed out how the predominantly negative treatment received by people with dementia in our 'hypercognitive' society may undermine their self-image and sense of worth and, therefore, result in 'excess disability'. Proper care for people with dementia stands or falls on taking their subjective experiences seriously, as well as on the search for a link in to their communication and interaction abilities. This may often lead to a relationship of trust where significantly more decisions about care and treatment can be shared than

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many healthcare professionals had previously believed possible. As part of this 'emancipatory process', it has now gradually become much more common to openly communicate about the diagnosis and significance of dementia with dementia sufferers themselves.

Shared decision-making and care planning

Herein it is very important to encourage 'shared decision-making' by involving next-of-kin and family members where possible at an early stage. This is, first of all, relevant because the sharing of information and decisions is the foundation of psychoeducation and palliative care. Dementia should not, after all, be reduced to a brain disorder with the individual as the sole person affected: it is a disorder that plays out in a social environment, affecting people in their most intimate relationships. It is not just people with dementia who are threatened with losing their identity; their partners also frequently experience a negative impact on self-image as a result of the dismantling of their relationship. However, in addition, the early involvement of next-of-kin is important for establishing a basis for shared aims for future decisions and the planning of care, also referred to as 'advance care planning' (ACP). ACP is a central pillar of good dementia care and can be defined as a dialogical process of supporting affected people and their proxies to think ahead and formulate goals of care as they confront the challenge of a progressive illness trajectory (Messinger-Rapport et al., 2009; Gillick, 2010; Hertogh, 2010). ACP needs to be firmly rooted in doctor-patient communication. It involves clarifying the health status of the person with dementia, determining his or her needs and values, and the subsequent development of treatment plans based on jointly set goals. Two recently developed consensus definitions underscore the relevance of viewing ACP as a dynamic process, encompassing regular reassessment of these goals and plans, in order to accommodate for changes in health and/or in personal values (Sudore et al., 2010; Rietjens et al., 2017). In dementia, the role of family and dear ones will become of increasing significance in ACP as the disease process develops. This will involve decisions around the aims and the limitations of care and medical treatment. Those ethicists who are fearful of paternalism might argue that an early involvement of other parties represents a potential breach of privacy and autonomy. Indeed, in practice, it does occur that some people with dementia insist on secrecy and confidentiality, and occasionally healthcare staff members have no other option than to respect this request (Schermer, 2001). But quite often, people prefer to share the burden of decision-making with others and—more importantly—next-of-kin are much better able to act in future decisions in the spirit of their loved ones' prior wishes and preferences if there has been joint consultation early on in the process. In other words, *shared* decisions set the foundations for *surrogate* decisions at a later stage. This leads us to the concept of competence.

Competence and decisional capacity

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Respect for autonomy in medical practice is primarily realized, as alluded to earlier, by involving patients in decisions about treatment and care. This process should satisfy two conditions, one external and one internal. The first concerns the quality and adequacy of the information. The second involves the capacity for decision-making. Patients will be unable to make informed decisions if they do not possess information that is relevant to the issue; however, they will also not be able to do so if they have the information but not the mental *capacity* to arrive at a judgment based on this. This capacity is usually referred to as *competence*. Although both terms are frequently used interchangeably (and are in the following sections), under some jurisdictions, 'competence' refers to a formal judicial determination concerning an individual's legal authority to make his or her own decisions, while 'capacity' refers to an evaluation made by health professionals about the functional abilities of patients (Kapp, 1995).

In ethical terms, competence lies somewhere between the principles of autonomy and beneficence (Welie, 2008). Considerations about competence or capacity play a role in searching for the right balance between both principles: the principle of respect for autonomy means that a person's wishes and views cannot simply be ignored. Too lightly doubting someone's competence may result in an unjustifiable restriction on his or her autonomy. On the other hand, holding on to competence too rigorously may result in a patient being put into a position where he or she is not adequately protected.

In clinical practice, the question of competence primarily arises in situations where care staff members are confronted with the question 'Has this (intended) decision been properly considered by the person to warrant it being respected?' The question about competence is, therefore, primarily one about what constitutes 'good' decisions. This highlights the fact that one is not dealing here with a purely clinical problem, but rather a normative judgment, where the physician is given the ultimate responsibility to determine whether or not to accept patients' rights of autonomy in terms of their decisions—nothing more and nothing less. Many shrink back from this responsibility, and this leads to a frequently expressed need among physicians for a greater level of support or more concrete guidance when dealing with issues involving competence and its assessment.

In recent years, numerous ethical and legal studies have been devoted to these subjects, including attempts to produce a better operationalization of the concept (Schermer, 2001; Welie, 2008; Kim, 2009). There is now a reasonable consensus that competence is not a personal characteristic (of people with a particular diagnosis), but rather an evaluation linked to the quality of a decision or choice within a specific context. After all, each decision is different, and complex decisions require greater numbers and different types of skills than simpler decisions. However, in practice, it is not just about the complexity of the decisions, but also and primarily about their practical consequences. For instance, there would be no need

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for healthcare staff to question a person's competence within an extremely complex decision if there were no consequences tied to it. Healthcare professionals are confronted with this issue as the consequences of respecting a decision become more far reaching and the criteria they set in judging competence become more stringent as the stakes get higher. This is often referred to as the *risk dependency* of competence. For instance, should a person refuse to comply with noninvasive potentially life-saving treatment (e.g. antibiotics for a severe lung infection), higher criteria will be set on his or her level of competence than where treatment refusal does not have serious consequences. A second aspect of risk dependency is the implied *asymmetry* of competence that this entails: agreeing to a medically indicated treatment is considered differently to refusing the same treatment, and this applies more as the stakes get higher. Based on this reasoning, physicians would be more justified in assuming competence where patients request or agree to life-saving treatment than when refusing treatment. Within the ethics literature there is an ongoing debate about the asymmetry of competence. Opponents of this theory have suggested that competence concerns patients' psychological functions. Whether or not these functions are adequate, they argue, may be influenced by the type of decision, but not by the outcome of the decision. This is certainly a tenable argument in theory, but, in practice, care professionals have to deal with the consequences of decisions taken, and sometimes they have to intervene to prevent patients from harming themselves.

As previously discussed, the risk dependency of competence means that the threshold for capacity increases as the consequences of the decision become more significant. This leads to the need for appropriate criteria for assessing (sufficient) competence. It also means that appropriate estimates need to be made in terms of the nature of risks that justify a formal evaluation of competence. The first question concerns 'how' and the second concerns 'when' an evaluation should be made. We only address the second question here; Chapter 52 and Chapter 58 cover the assessment of competence/capacity, respectively, in more detail.

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When is an evaluation of competence indicated?

It must be said from the outset that a formal evaluation of competence may be burdensome to a person with dementia, and may not always be useful in the context of long-term care. After all, due to the progressive nature of the disease, care and treatment goals constantly have to be adjusted, and the patient's level of competence is anticipated to be gradually decreasing. More important in this connection than evaluating competence is that healthcare staff members remain well aware of a person's remaining abilities in order to enable and 'empower' them to make choices about aspects of care with the right support. In a general sense, the following guidelines may be employed in assessing *when* a formal evaluation of competence is indicated:

- In principle, the care relationship is built upon an assumption of competence. Hence, the decision to make a formal evaluation is not taken lightly. As described previously in this chapter, a person-centred approach implies that staff take each person's experiences and levels of comprehension into consideration, for instance by using comprehensible explanations. There are, of course, limits to simplifying information and providing it piecemeal. This is encapsulated in the term 'appropriate' information, which should, at least, comprise the nature, aim, and consequences of (not implementing) the proposed treatment. If these minimum standards cannot (or can no longer) be satisfied it may lead to doubt as to the level of competence of the person with dementia. Whether this doubt justifies a formal evaluation depends on the following guideline.
- There should always be a 'clear indication' for a formal evaluation of competence, and the burden of proof in this rests with the healthcare professional. Any doubt about the competence of a person with dementia on the part of care staff is, therefore, in itself not sufficient: it should also be related to the consequences of the decision that the person is taking or intending to take. Thus, a formal evaluation of competence is only justified where a behaviour or decision has 'significant consequences'.

Therefore, a person with dementia should be allowed the 'freedom' of choice in many decision scenarios where there are 'no significant consequences', even if there is reasonable doubt as to his or her competence. The advantage of this approach is that people do not have to prove, as it were, their competence for each decision. Some authors have criticized this approach as it is ultimately still healthcare staff who determine what the 'significant consequences' are, which may mean that there is still a level of paternalism lurking in the background. However, the reasoning behind this approach fits well with the views concerning proper care that are prevalent in practice. It has been shown, for example, that formal tests of competence are used infrequently and only used in borderline situations, where there is conflict or an unbridgeable divide between patient and staff perspectives. Therefore, choosing

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‘shared decision-making’ with adequate decision support for people with impaired decision-making abilities, rather than steering towards a formal competency test, has much to recommend it (Hertogh, 2004; Peisah et al., 2013). This approach offers the option to incorporate the values, life history, and emotions of a person with dementia, as well as contextual factors, into the decision process. It then often becomes apparent that it is not necessary to establish whether or not someone is competent to take the required decision, which not only bypasses many procedures, but also prevents the person with dementia from being ignored in a more or less intrusive manner.

In summary, although there is much good to be said for the notion of competence, formal evaluations of competence should be reserved for borderline and conflict situations where people are sometimes forced to resort to these judgments in the absence of alternatives or where ‘shared decision-making’ has failed or does not appear to be an option. However, such an evaluation is made and underpinned, the result can never be construed as a statement of fact, for such an assessment of competence will ultimately always involve a normative ethical judgment.

Written advance directives and the representative’s role

In situations where people are no longer able to be involved in decisions about their care and treatment, others will act on their behalf as their representatives (or surrogate decision-makers). Who is able to act in this capacity and how this representation is shaped is governed—in most countries—by law. It should be noted that the authority of representatives may differ by country. For instance, in the Netherlands, a representative may not assume responsibility for the most personal decisions of the individual he or she is representing, and the level of responsibility imposed on physicians for those medical decisions being considered with a representative is greater than the responsibility taken directly through consultation with the patient.

It is of primary importance that a representative, in carrying out his or her task, focuses on the represented person’s best interest. Representatives should not allow themselves to be guided by their own views about what is the best and most desirable course of action. It is often believed that a written AD may be of use here in ascertaining the former views of a person who is no longer competent. From a legal perspective, a document like this is the strongest instrument by which someone may attempt to maintain control over care situations and treatment decisions in the event of incapacity, and an increasing number of countries are moving towards anchoring ADs in national law (Hertogh, 2011).

The issue seems, in fact, quite simple: as long as a person is competent, the physician will tailor care directly to suit that person; once the person is no longer able to make known his or her wishes, then the written AD is considered to represent their ‘actual’ wishes. In combination with the

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proper regulation of representation/surrogate decision-making, the rights of an incompetent person thus appear to be adequately safeguarded. In practice, however, this 'simple' solution may lead to a number of ethical problems.

The dilemmas of the directives

A widely accepted definition describes ADs¹ as:

written instructions executed by decisionally capable adults that pertain to future medical treatment preferences of the party executing the document. These directives take effect only if the patient is decisionally incapacitated at the time that specific decisions need to be made (Kapp, 1995).

ADs can be classified into two categories: treatment directives and proxy directives. A treatment directive (often called a 'living will') refers to a document specifying what kind of treatment the author desires under specific conditions in the event of incapacity, while a proxy directive empowers another person (e.g. healthcare proxy or durable power of attorney) to make decisions on behalf of the author. Both types of directives can also be combined (de Boer et al., 2010). Of relevance here is that most jurisdictions only recognize the so-called negative treatment directive, i.e. a directive containing a refusal of specified treatments in advance. Positive directives, specifying what treatments one would want to receive in case of incapacity, are never legally binding.

Morally, ADs are rooted in the doctrine of informed consent. With expanding technology, they became a key issue of the autonomy-based bioethics movement of the 1970s. In case of incompetence, when contemporaneous autonomy is no longer possible, so-called precedent or prospective autonomy in the form of previous statements and expressed beliefs relevant to the treatment issues at stake should govern the outcome (Dresser, 1992; Winzelberg et al., 2005).

When first introduced (in the US in the course of the 1990s), the enthusiasm for ADs was largely ideological. Empirical knowledge on the subject was largely unavailable at the time and it was more or less taken for granted that ADs would have a positive effect on medical culture and decision-making.

With experience, however, came awareness of the problems, and gradually empirical research revealed that the reality was far from what proponents of ADs had expected it to be, adding to a growing consensus on the failure of ADs (Hertogh, 2011; Perkins, 2007; Fagerlin, 2004).

Since the disappointing findings of the first empirical study into the practice of ADs, the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) (Connors et al., 1995), a plethora of research articles and critical reviews have been published and multiple interventions were designed to stimulate AD completion,

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including several attempts to redesign ADs in order to increase their practicability and relevance to decision-making. Of the problems that all this research has revealed, some are more practical, while others are more fundamental in nature.

First of all, the overall frequency of ADs continues to be low, notwithstanding the existence of legal rules encouraging the completion of directives, such as the Patient Self-Determination Act in the US that came into force in 1990. Approximately one in three US adults has completed an AD (Yadav et al., 2017), but outside the US much lower rates are reported, with a maximum of between 8–10% in the Netherlands (van Wijmen et al., 2010), Germany (Evans et al., 2012) and the UK (Aw et al., 2012). Next, when they are completed, the instructions contained in an AD are often vague or ambiguous, as a consequence of which they are often not honoured (Teno et al., 1997). The concept of advance care planning (ACP) deals with this problem by stimulating consultation with health professionals when one considers drafting an AD.

However, it does not exclude situations in which an AD may conflict with what physicians or surrogates view as a patient's best interest, potentially creating confusion, ambivalence, and/or burden among surrogates and physicians (Smith et al., 2013). There may be circumstances which make it more ethically defensible to override an AD and to respect a person's goals and values rather than following the exact preferences in the directive (Bruce et al., 2016; Sudore et al., 2010; Sulmasy et al., 2010; Winzelberg et al., 2005). Evidence on whether authors want their ADs to be strictly followed or to serve as general guidelines is conflicting and provides no guidance here (Sehgal et al., 1992; Jox et al., 2008). To further complicate matters, it has been shown that proxies do a poor job in interpreting ADs, as they are frequently biased by their own treatment preferences (Fagerlin et al., 2010). Furthermore, the most poignant problems of advance statements pertain to the (in)stability of preferences over time: it is well known that our anticipatory beliefs often fail to recognize our ability to adapt, and that it is extremely difficult to imagine how one's current preferences will hold in a situation (like dementia) one has never really experienced (Hertogh et al., 2007). In general, preferences for life-sustaining treatments are probably most stable in people with a stable health condition. Unstable health, on the other hand, will lead to changing preferences. This phenomenon is often so marked that it has been termed 'the disability paradox': a life that was once despised before the advent of chronic disease, is accepted and even embraced with advancing illness (Albrecht and Devlieger, 1999). With changing circumstances, people change their point of reference. Dementia is no exception to this 'rule', as is testified by a growing body of research on living with dementia from the affected person's perspective (de Boer et al., 2007). People do not develop dementia overnight; instead, the gradual course of the disease allows for adaptation and response shift. But what if they forget to change their AD, or are no longer able to do so? Here we touch upon a key obstacle for complying with ADs.

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Therefore, a move on from static ADs to the more dynamic practice of ACP is taking place, as outlined in the section 'Shared decision-making and care planning'. Although more research is needed, there is evidence that ACP positively impacts the quality of end-of-life care, and that complex ACP interventions may be more effective in meeting people's preferences than written documents alone (Brinkman et al., 2014). Preference stability for end-of life decisions seem to be larger in those who engage in ACP (Auriemma et al., 2014). It must be emphasized, however, that the process of ACP should be flexible and sensitive to a person's views on autonomy. Not everyone desires to manage and control his or her future. Some people prefer to live life one day at a time and many wish to share the burden of decision-making with others, or even delegate this responsibility to their families and health professionals. It follows that this approach to ACP is time consuming and calls for high quality communicative skills, as well as for a preparedness of doctors to take on a (pro)active role, using their knowledge of the disease trajectory in a tailored way. The framework of a palliative care policy can offer guidance here to people with dementia, their families, and health professionals (Hines et al., 2011).

Palliative care

The issue of so-called non-cancer palliative care has received a lot of attention recently. However, the proposal to conceptualize the care of people with dementia from a palliative care perspective had already been put forward within nursing home medicine in the Netherlands in the 1990s, and with good reason (Hertogh and Ribbe, 1996).

Dementia is, after all, an incurable and ultimately terminal condition. Curative, disease-specific therapy is still not available. Medical treatment is, therefore, limited to alleviating symptoms and complications of dementia, and prolonging life is primarily a consideration in terms of interventions for comorbidities and concurrent disorders. As the disease progresses, questions concerning the aims and limits of medical interventions become more frequent, necessitating a constant search for the right balance between under- and over-treatment. For that reason, it is of great importance to arrive at clear, tailored agreements as a part of ACP. As said, this plan should be periodically re-evaluated and amended if required in line with the disease's progression and important developments within this process. Where possible, this should involve the person with dementia, but in the more advanced stages of the disease—and, therefore, in the majority of people with dementia admitted to nursing homes— treatment planning will be discussed with surrogates. The palliative care concept provides a framework within which this discussion about the aims and limits of medical care may take place and within which ethical questions and treatment dilemmas that have arisen may also be considered and addressed. In Dutch nursing home medicine, this approach is based on the original definition provided by the World Health Organization (WHO, 1990) (see Box 53.1).

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Box 53.1 Palliative care

Palliative care is integral multidisciplinary care for patients with incurable diseases, aimed at reaching and maintaining optimal quality of life for both patients and their relatives. More specifically, palliative care:

- Affirms life and regards dying as a normal process;
- Neither hastens nor postpones death;
- Provides relief from pain and other distressing symptoms;
- Integrates the psychological and spiritual aspects of patient care;
- Offers a support system to help patients live as actively as possible until death;
- Offers a support system to help the family cope during the patient's illness and in their own bereavement

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Of note, a palliative care approach is not exclusively associated with (terminal) end-of-life care. It also comprises care for people who may have a terminal illness but have not yet reached the terminal phase of their disease. Furthermore, within this WHO definition, palliative care also has a place for people with chronic illnesses where long-term management or suppression of the disease is not (or no longer) an option.

The type of care offered to people with dementia in nursing homes is, in essence, palliative in nature and orientation in the broad sense intended here. The focus of this care is on maintaining the best quality of life possible, and extending life should never become a goal in itself. Intuitively this is a clear aim. However, translating it into practice is not always evident. A palliative approach that focuses on maximization of comfort and relief of suffering can be or cannot be combined with treatment of intercurrent illnesses that may prolong life. This approach fits well in the recently proposed model of palliative care for people with dementia (see Fig. 53.1), published on behalf of The European Association for Palliative Care (EAPC) in the White Paper 'Defining optimal palliative care in older people with dementia' (van der Steen et al., 2014). Based on evidence and consensus, the EAPC identified eleven domains for palliative care and defined optimal care for people with dementia.

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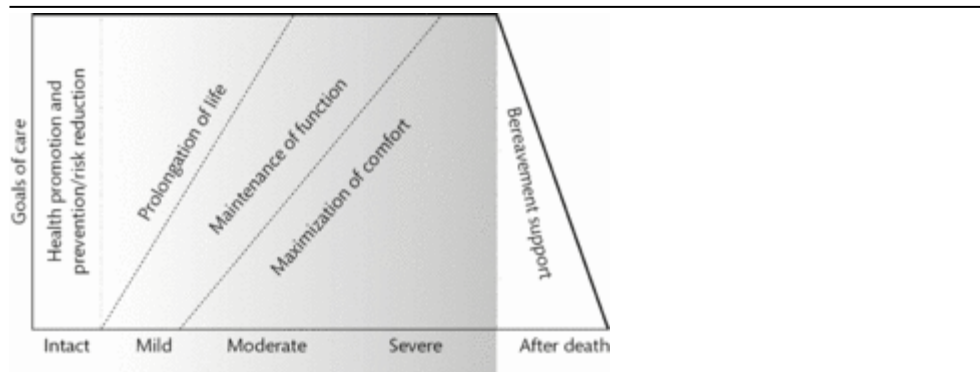


Fig. 53.1

Model of changing care goals.

Reproduced from Van der Steen, J.T., et al. White paper defining optimal palliative care in older people with dementia: a Delphi study and recommendations from the European Association for Palliative Care. *Palliative Medicine*, 28(3); 197–209. Copyright © 2014, SAGE Publications. <https://doi.org/10.1177/0269216313493685>.

Quality of life and palliative care

The term ‘quality of life’ has diverse interpretations. In political theory, it is normally related to the material and socioeconomic circumstances in which people live their lives, or to the opportunities they are offered by society to realize a good life (Nussbaum, 2006). Health-related quality of life is frequently defined as the subjective way in which a person appraises his or her present state of life. However, a clear, conceptual definition of health-related quality of life is missing. Researchers have nonetheless tried to make quality of life measurable through the development of several multidimensional questionnaires. So, what is available are operational definitions, which in essence boil down to quality of life as measured on this scale or through that instrument. What is clear, though, is that health-related quality of life does not reflect an external description of an objective entity, but rather a subjective evaluation by the patient of the relevant aspects of his or her health. These types of self-assessment scales have also been developed for dementia, occasionally based on prior, qualitative studies of people with dementia or their carers. An extensive discussion of the methodological aspects of these types of instruments is beyond the scope of this chapter, but it is important to establish that their usefulness diminishes with advancing dementia. We may even ask ourselves whether the concept of quality of life is in itself appropriate in the more advanced stages, since a direct, subjective assessment, of and by the person with advanced dementia, is no longer an option here. The option that does remain is behavioural observations as an indirect measurement. On this basis,

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observational scales for quality of life in advanced dementia have been developed, such as the QUALIDEM scale (Ettema et al., 2007).

However, the persistent use of the term ‘quality of life’ obscures the presence of another construct, and an observational scale such as this also has a normatively different status than a self-assessment scale. Caution is required here for two reasons. First, research has shown that people with mild to moderate dementia shift their values and priorities in life, and there is no reason to assume that this process of response shift extinguishes in later stages (Hertogh and Ribbe, 1996). Second, other research suggests that caregivers have a tendency to report lower scores on quality of life than people with dementia themselves. This ‘perception gap’ is probably the combined effect of an affected person’s response shift, and caregiver bias as a result of their care burden (Sands et al., 2004). The conclusion, therefore, must be that the term quality of life is applied with a necessary amount of caution in the care of people with advanced stages of dementia, where quality of life appraisals are necessarily based on observations and interpretations by others than the person him/herself. In practice, care and treatment will be primarily focused on a person’s wellbeing or (dis)comfort. For example, nursing home residents with dementia frequently have burdensome symptoms such as pain and these burdensome symptoms frequently persist over the disease trajectory, with a peak shortly before death (Hendriks et al., 2015, 2014).

Observational scales for discomfort, counting frequency, intensity, and duration of behaviour, such as the Discomfort Scale—Dementia of Alzheimer Type (DS-DAT), pose a different and less value laden approach and may be of some assistance here (Hurley et al., 1992). Similarly, there are dementia pain scales observing behaviour directly during a few minutes, such as the Pain Assessment in Advanced Dementia (PAINAD), and those rating behaviour over the last week, for which familiarity with the affected person is required, such as the Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC) (Warden et al., 2003; Fuchs-Lascelle and Hadjistavropoulos, 2004). However, the end estimations of a person’s state of wellbeing strongly depend on (formal and informal) caregivers’ appraisal of behaviour and nonverbal communication, which are always more or less biased by their own situation and their emotional ties. This dilemma needs to be addressed openly as an integral part of palliative care and ACP.

Prolonging life

When talking about life-prolonging treatment, it is important to make the distinction between the intention and the effect of medical treatment. Although prolonging life is not the aim or intention of medical treatment in the context of palliative care, it does not mean that palliative medical treatment cannot or should not potentially lead to a prolongation of life as a side or co-intended effect. It is highly likely that people with dementia will live longer as a result of treatment that is primarily aimed at

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maintaining or improving their wellbeing. A person with cancer for whom meaningful life extension through disease-specific treatment has become an illusion, but who is not yet in the terminal stages of his or her disease, is certainly still entitled to antibiotic treatment for a respiratory or urinary tract infection, and, furthermore, regular monitoring and adequate control of his or her blood sugar levels will not be omitted should he or she also be diabetic. The aim of this is not to keep someone alive as long as possible, but rather not to burden the last phase of life with, in principle, readily treatable discomfort, even if the medication used has the potential side effect of extending life. However, it is advisable to evaluate critically the use of preventive medication. After all, medication used for primary or secondary prevention may have a time-until-benefit extending beyond a person's actual life-expectancy. Therefore, treatment with this type of medication must be critically assessed and may be best discontinued (Holmes et al., 2006; Hendriks et al., 2017a).

There is, in principle, no reason for treating individuals suffering from incurable and progressive dementia differently. Still, there are important differences compared to the situation of someone with cancer. The root of this lies in the problem of a decline in communication possibilities and the increasing lack of competence of patients with dementia. In the advanced and terminal stage of the disease, signs of (dis)comfort can only be derived from observations. Furthermore, as the disease progresses, the issue of whether the life-extending side effects of palliative treatments are still morally acceptable becomes a more significant question. After all, any successful treatment of a respiratory tract infection or other potentially life-threatening development exposes a person to a further progression of his or her dementia, along with the associated mental and physical decline. Hence, instead of asking what constitutes good quality of life, the question more and more becomes how to arrange for a good quality of dying. Discussion of this question with surrogates in the context of ACP may lead to a more restrictive treatment policy, focusing on comfort care only. If planning was started well in advance, this decision may be well prepared for and relatively easy to make (Hendriks et al., 2017b). Research suggests that informing nursing home residents and families about the course of dementia, the short average survival time, burdensome symptoms that can occur, and the occurrence of pneumonia and intake problems, which have a poor prognosis, may help formulate realistic overarching care goals to help prevent burdensome, unnecessary treatment in acute situations. (Hendriks et al., 2017b, 2017c, 2015, 2014). However, it remains an important responsibility of the physician to choose the proper moment. He or she should have the sensitivity to recognize how and where in the course of the disease trajectory an additional disease or complication offers an opportunity to arrange for—from a palliative care perspective—an acceptable end-of-life scenario by abstaining from life-sustaining treatment and focusing on active symptom control only. This, however, implies that a particular responsibility rests on the physician, together with the family/representative, since here,

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more so than in other domains of palliative care, it is in effect the physician and the representative who direct the actual end-of-life scenario. In taking on this responsibility, surrogates as well as care professionals can find support and guidance in decision aids and written information on the course of the disease, the complications to be expected, and the burdensome decisions the illness trajectory holds in store for them: for example, regarding the use of antibiotics, feeding tubes, and artificial (re)hydration. In this respect it is worth noting that the evaluation of a booklet on comfort care in end-stage dementia demonstrated that written information on the options of palliative and comfort care are welcomed, not only by family members and surrogate decision-makers, but also by practitioners and—in particular—by nurses (van der Steen, Arcand et al., 2011; van der Steen, Toscani et al., 2011). Through such written decision support instruments, all parties feel better equipped to address the ethical issues at stake and engage in shared decision-making and care provision.

Conclusion

This chapter has discussed a number of ethical questions arising in the care of people with dementia. The progressive nature and consequences of the disease for the individuals affected and those in their environment require specific ethical deliberations and a focus on shared decision-making and (advance) care planning. Prevalent rights-based ethics do not always offer the most appropriate guidelines within this context and may even occasionally create new ethical problems, as is the case with ADs. Apart from refining current views on autonomy, additional guidelines are required from a person-centred ethics of care perspective to help make relevant decisions about (current and future) care and treatment.

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Notes:

1 This section is a Adapted from Hertogh, 2011



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Carers and dementia

Chapter: Carers and dementia

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Introduction

People living with dementia inevitably need increasing support as dementia develops and progresses. The bulk of this support is provided by family members, who often step into caregiving as a matter of course and, over time, take on more responsibility until many are full time carers. Family carers are of vital importance to the quality of life of many people living with dementia and to sustaining their ability to live in their own home in the community (Smits et al., 2007). When assessing care and support needs, family carers need to be explicitly considered. Carers need to be given the tools, in terms of information, skills and support to take on caring, and be supported to continue over time as care needs change or expand. Taking on caring responsibilities has a far-reaching impact whether physical, psychological, social or financial. So, carers may require emotional and practical support to care in a way that minimizes

the impact on their own health and avoids placing their own wellbeing at risk.

In this chapter, we aim to provide information about dementia caregiving that is useful to health care professionals, to raise awareness of carer issues and to give evidence-based ideas about how to involve and support carers effectively as they care for their relatives. The chapter opens with an overview of the extent and nature of family caregiving, followed by information about the impact of caregiving on carers and the caregiving trajectory over time. We introduce models that provide a useful way of formulating the issues to help planning care to meet the needs of carers encountered in practice; and we summarize the research evidence regarding interventions that are helpful to carers.

Facts and figures

There are approximately 46 million people living with dementia worldwide and this is estimated to cost the global economy £450 billion per year (ADI, 2010). Within the UK, there are 24 million people who know a family member or friend with dementia (ADI, 2010). A report by Alzheimer's Research UK in 2015 revealed that there are approximately 700,000 family members actively providing care and support, worth £8 billion per year, for a relative with dementia. This is half of the dementia care provided in the UK (National Dementia Strategy, 2009). A more recent UK-based survey by the Alzheimer's Society (Alzheimer's Society, 2017) found that 87% of 966 people living with dementia were assisted by family members, whereas only 14% had help with their day-to-day life from a paid carer. Figures from the US suggest that families and friends provide about 18.1 billion hours of care at a cost of over \$221 billion (Alzheimer's Association, 2016). As well as providing economic benefit, research suggests that having a co-resident carer can improve the person living with dementia's quality of life (Farina et al., 2017) and can produce a twenty-fold reduction in the risk of institutionalization (Banerjee et al., 2003).

It is estimated that 39% of carers spend over one hundred hours per week providing care and support, a level which has been found to predict negative carer outcomes (Alzheimer's Research UK, 2014). However, it is worth noting that the more time spent providing care can also increase the number of gains a carer experiences in their role (Parveen & Morrison., 2012). Women are more likely to provide care for a relative with dementia, with figures suggesting that 60 to 70% of carers are female (ARUK, 2015). Women are also more likely to provide support for more than five years. Responsibility for caregiving tends to fall upon spouses, followed by daughters, daughters-in-law, and sons (Aneshensel et al., 1995; O'Rourke et al., 2000). Although carers provide a significant amount of support for those living with dementia, it is striking that 44% of carers themselves are living with a chronic illness or disability (ARUK, 2014). Approximately 61% of carers state that they lack support from other family members, friends, and dementia services (ARUK, 2015).

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Busy health and social care providers may over-estimate the reach of support provided by services but surveys of this sort show how vital family carers are and therefore how important it is that family supporters are considered whenever care is being planned for someone with dementia.

Currently 58% of people living with dementia reside in low-income countries, a proportion predicted to increase to 71% by 2040 (Prince et al., 2013). Whereas there is an expected 100% increase in prevalence in developed countries, there will be a 300% increase in countries such as India (Prince et al., 2009). Formal care may not be widely available in such countries and family members traditionally provide support for those with care needs (Ahmad, 1996; Katbamna et al., 2004). Family care indeed accounts for 56% of societal costs in low-income countries (Wimo et al., 2007) and family carers are at an economic disadvantage. The 10/66 Dementia Research Group (Prince, 2000) report that family carers in low income countries are forced to cut down on paid work yet compensatory benefits are non-existent within these countries' welfare systems. Considering the expected increase in the number of carers being relied upon to provide support for relatives, there is an urgent need to develop services in low-income countries that will support families to continue to care.

Carers—basics

The term carer or caregiver is difficult to define as it is used in different ways by health and social care professionals and families. The term 'carer' is more commonly used by UK care-based organizations, whereas the term 'caregiver' is more often used in the American context. Carers Trust in the UK defines a carer as an individual who provides care and support without financial compensation for a family member who due to illness, disability, a mental health problem, or an addiction cannot cope without support. Similar definitions can be found within the research literature, although the term 'informal carer' is often applied to family members. The problem with this term is that it implies the care provided by family members is casual and perhaps of not high quality. The term has therefore not been favoured by carer services and carers themselves (Farina et al., 2017).

Although the term carer is widely used by health care professionals and service providers, it can be problematic when used while talking to families. Most caregiving relationships are extremely complex, as they are based upon long shared histories, for example, marriage. Many family members therefore don't perceive themselves as 'carers', but as wives or daughters (Parveen et al., 2011) and provide support as a natural part of community or family life. The term also places emphasis on the care partners as 'helper' and 'helped', whereas in some relationships, e.g. spouses, the care is a mutual exchange of support. Within the context of dementia, the term can place the person with dementia as 'cared for' and thus undermine his or her independence and identity. Despite the

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limitations of the term, it can be useful when used in connection with carers' assessments, registers and groups, but should be used sensitively.

Who provides care is often influenced by the position of the person with dementia within the family, as well as by availability and according to culture. The spouse is the most likely person to provide care and support, and if a spouse is not available or requires additional support from family members, daughters, and daughters-in-law usually step in. As caregiving is predominantly a female role, sons often find themselves in a minority. Spouse caregivers may not consider that they are providing care per se but simply acting out of mutual marital obligations. Filial carer is a term used to describe adult children or children-in-law providing care for a parent/parent-in-law. Non-kin carers include neighbours and friends providing unpaid care and support in the community.

The support provided by carers is wide ranging. Nolan and colleagues (1996) describe the following types of caregiving: anticipatory care, preventative care, supervisory care, preservative care, instrumental care, protective care, reconstructive care, and reciprocal care. These types of care are thought to overlap considerably. Nolan and colleagues (1995) state that by providing a typology of care, health care professionals are enabled to provide services to be facilitative, rather than obstructive.

Impact of caring

Caring for a relative with dementia impacts on carers' lives in many ways. Witnessing decline in a relative frequently changes the nature of the relationship, causing grief, anxiety, or emotional upset. In addition, taking on extra tasks and responsibilities may have an impact on sleep, energy levels, physical health, and time available for work, hobbies, and social life. Yet, many family members who become carers gain satisfaction from fulfilling their vows and values and from the opportunity to develop new skills or discover previously untapped personal qualities.

Impact on fulfilment of needs

In a recent study of how caring facilitated or impeded fulfilment of carers' needs (Pini et al., 2017), a thematic analysis of interviews with a diverse sample of 42 current carers of a relative with dementia produced nine themes. These themes, shown in Table 54.1, highlight the impact of caring on the relationship between carer and cared-for, as well as demonstrating that the carer may feel he/she lacks control over his/her own life in the face of caring for someone with dementia. The themes also show that caring often impacts on the carer's sense of identity and ability to connect with others.

Table 54.1 Nine key themes on the way caring for a person with dementia impacts on fulfilment of the carer's own needs.

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Being a carer impacts on fulfilling my need to/for ...	Illustrative quotes of the way caring impacts on the need.
feel close to my relative	You've got to find those little glimmers, those little moments where you get the person back just briefly. Those little glimmers, and you just think, 'Oh right, yes, that's how it was ... It's bittersweet, isn't it?' (Abbie).
feel in control	I think if you look too far into the future you frighten yourself and wonder how you will cope, and I genuinely don't think too far ahead (Theresa).
freedom	I feel I'm attached on a piece of string to my husband and that string is getting shorter and shorter and shorter (Beatrice).
feel connected to the people around me	They're my medicine, my friends (Beatrice).
protect my relative	When I see her in those moments when she's like a child or when she's lost and she's looking to me to guide her, just those few moments then everything becomes secondary and I just think, I'm going to help you and that's all there is to it (Karl).
take care of myself	I've not really focused on my own physical, well physical and mental health needs so, I find that, you know, health problems have cropped up all of a sudden, that needed my attention but I was, you know, not paying attention on that side and focusing on my mum (Jayda).
be my own person	I would go mad if I wasn't working. I think you have to; I think if you can maintain some normality, you're also looking after yourself, I suppose it's like putting your life jacket on first isn't it before you deal with your child (Charlotte).

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share/express my thoughts and feelings	It's almost a self-protection thing, isn't it? Maybe it's just me, some things you just keep, keep closed because it's, maybe you make yourself vulnerable to, if you say something in an unguarded moment, you can't take it back (Abbie).
get things done	Some days all those plates come crashing down at the same time, 'cause the plates stopped spinning. Fortunately, it's rare, but it can happen and when it does happen then, yeah, I have a meltdown (Isobel).

Source: data from Pini, S., Ingleson, E., Megson, et al, 2017. A needs-led framework for understanding the impact of caring for a family member with dementia. *The Gerontologist*.

Impact on relationships

Reviews of research on the effects of dementia on family relationships indicate that dementia makes communication more difficult and takes away opportunities for shared activities (Ablitt et al., 2009; La Fontaine and Oyeboode, 2014; Quinn et al., 2010). Such changes often lead to grief, with almost 75% of carers experiencing grief related to the diagnosis, the loss of past roles of the person with dementia, and the loss of intimacy (Diwan et al., 2009; Sanders and Corley, 2003). Where children or young people are involved, as in many cases of young onset, they may find having a parent with dementia a very difficult experience, as shown in a recent study of 19 children and young people, aged 8–31 years, with a parent with dementia (Hall and Sikes, 2018; Sikes and Hall, 2017). In families where one parent had young onset frontotemporal dementia, 75% of parents reported their children experienced conflict with the parent with dementia, had problems at school, and suffered psychological/emotional problems (Passant et al., 2005).

This evidence indicates the need for health care professionals to pay attention to the relational aspects of caring as well as the practical aspects, and reminds us that health and social services not only need to consider the role and wellbeing of the primary carer, but also the respective roles and wellbeing of the wider family. The latter may be especially pertinent when considering young onset dementia, since young people may be involved in caring, and it is also of relevance when supporting families from cultures that have more extended family structures, such as those from 'black and minority ethnic' populations, since in these families caring may be more often shared between a number of relatives.

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Positive impacts

Although approximately 50% of primary carers experience high levels of burden (Brodaty et al., 2014), it is worth remembering the corollary of this: that therefore about 50% do not. Many carers report that, despite some distress or stress, love and happiness often remain (La Fontaine and Oyebode, 2014; Ablitt, et al., 2009; Quinn, et al., 2010) and some carers report that they have developed a closer relationship as a result of caring (Netto et al., 2009). Many carers find that supporting their relative with dementia gives them a sense of pride, satisfaction, or fulfilment. Some develop new skills or find that caregiving leads to personal growth (Sörensen et al., 2006; Lloyd et al., 2016). In a review of 14 qualitative studies aimed at understanding positive aspects of caring for someone with dementia (Lloyd et al., 2016), the authors propose that positive facets of caregiving have been found to relate to: role satisfaction (from doing a good job in ensuring the person is well cared for and safe), emotional rewards (e.g. from feeling appreciated), relationship gains (from feeling close to the person cared-for), personal growth (e.g. developing a capacity for patience or becoming more self-aware), increased faith or spiritual growth, a sense of competence and mastery in the face of challenging circumstances, fulfilling a sense of duty, and 'giving back' to the person being cared for.

Positive caring experiences seem to be more likely in those who are committed to the relationship, who find a way of accepting the changes dementia brings, and who make a conscious effort to see things positively. In addition, carers who find ways of creating opportunities for the person with dementia to take part in activities, and those who have ways of drawing strength from faith, social support, or their own past experiences, seem to be able to remain positive (Lloyd et al., 2016). Among spousal carers, those who believe the person with dementia and the relationship are essentially the same as they used to be seem to have more positive and fewer negative feelings (Riley et al., 2016). Ott and colleagues (2007) conducted a quantitative study with over 200 dementia carers focusing on personal growth in particular and found that 46% of the variance in levels of positive growth was explained by higher levels of social support, lower levels of depression and coping by reframing and by religion.

Not only is being able to adopt a positive perspective helpful to carers' wellbeing, but also carers who experience gains or satisfaction are less likely to move the people with dementia into care than relatives of those who feel burdened (Roff et al. 2004; Luppia et al., 2010).

Impact on mental and physical health

The negative impact of caring can produce mental health problems. In a review that summarized the current state of knowledge, Pinquart and colleagues (2006) synthesized the findings of several meta-analyses and concluded that 'carers of people with dementia have more symptoms of

depression, higher stress scores, lower self-efficacy, and lower subjective wellbeing than non-carers' (p. 962). In a systematic review of studies of depression in caregivers, Cuijpers (2005) concluded that there is evidence that over one in five carers becomes depressed and the odds of developing depression are significantly increased compared with non-carers. Conclusions from Schoenmakers and colleagues (2010) systematic review concur that dementia carers have higher levels of depression than non-carers or carers for those with other chronic or psychiatric conditions. They summarize past research as indicating 30–80% of carers are depressed. Unsurprisingly, higher levels of depression in carers are associated with higher health service usage (Zhu et al., 2015). Anxiety has been less researched but Cooper and colleagues (2007) reviewed 33 studies, and concluded that anxiety levels were higher among carers than matched non-carer control groups, with significant levels of anxiety affecting about 25% of carers. These relatively high levels of depression and anxiety suggest that professionals should routinely enquire about carers' wellbeing and be prepared to suggest treatment that may help where necessary.

Physical health can also be affected. The physical health of carers has been found to be poorer on average than the health of non-carers, and that of dementia carers has been found to be worse on average than that those supporting a relative with another health condition, even when the samples are age-matched (Sörensen et al., 2006). Pinquart and Sörensen (2003) conducted a meta-analysis of objective health from 39 studies, covering responses from over 3,500 carers compared with more than 12,000 non-carers and found that carers on average had poorer objective health than non-carers. They also found there were no significant differences between the findings of studies that used objective and subjective health reports. This implies that it is valid to ask carers how they feel about their state of health as a marker of whether the person is physically suffering from caring.

It is often assumed that how dementia affects family carers is related to the severity of cognitive or functional impairment of the person with dementia. However, correlational studies show this is not necessarily the case (Pinquart and Sörensen, 2003). How carers cope depends on the carer's physical and mental health and personality (for example, whether the person has a propensity to be anxious), the nature of their prior relationship with the person cared for, and the behaviour and specific care needs of the person with dementia (Ablitt et al., 2009; Brodaty et al., 2014; Joling et al., 2015; Lloyd et al., 2016). Coping with the behavioural issues of the person with dementia is consistently found to have more influence on carer outcomes than cognitive functioning and functional disability. In a meta-analysis of findings from 228 mainly American studies Pinquart and Sörensen (2003) found that behavioural issues, such as day and night-time restlessness of the person with dementia, and emotional or behavioural disinhibition, were moderate predictors of carer burden ($r=0.37$) and carer depression ($r=0.27$), respectively, whereas functional

impairment ($r=0.22$ and 0.14) and cognitive impairment ($r=0.18$ and 0.16) showed only small correlations. Whether the carer believes he or she has the capacity to cope (i.e. the carer's self-efficacy beliefs) also seems to be a major influence (van der Lee et al., 2014, 2017). These findings imply that interventions that enable carers to understand and respond effectively to the behaviour of the person with dementia and which enhance the carer's belief in his or her ability to cope have potential to be beneficial to carers.

Impact on particular groups

Much research into caring for a relative or friend with dementia has focused on white, female, spousal carers, caring for a relative with late onset Alzheimer's, vascular, or mixed dementia. However, caring poses different issues and has different meanings and impact for different sections of society, including men, and people of different cultural backgrounds or ethnicities, as well as for those caring for a relative with young onset dementia or a rare dementia, or looking after a relative with learning disability and dementia.

Ethnicity

Of particular relevance to caregiving experience in diverse multicultural societies such as modern Britain, the US and much of Europe, is ethnicity. Research has shown that, on average, those from minority ethnic populations receive their diagnosis of dementia later than the majority ethnic population, and have a different trajectory of care, being less likely to be prescribed medications for dementia and less likely to use residential or nursing home care (Cooper et al., 2010). The corollary of these patterns of care is that families are often caring for someone until a later stage of dementia before they have a diagnosis or access to services and support and also that many families continue to provide support in the family home, even when there is severe disability due to dementia.

Qualitative research, mainly with South Asian carers in the UK, has found that there is lack of awareness of the nature of dementia, with memory problems often seen as a sign of normal ageing rather than an early symptom of dementia (Giebel et al., 2015). Dementia may also carry a greater stigma in minority ethnic populations, being seen as a sign of madness or sometimes being explained by notions of possession or being seen as a 'white person's illness' (Berwald et al., 2016). Family carers may either share or have to contend with these illness beliefs, so may benefit from provision of accurate information. Many family members assume caring as a natural extension of family responsibility, and may feel pressure from other family members or the wider community to continue, despite their own feelings of stress (Johl et al., 2016; Tilkie et al., 2010, Parveen et al., 2017b, Berwald et al., 2016). On the other hand, some carers may feel less resentment or entrapment resulting in positive consequences for carer wellbeing, with research in the US consistently finding 'black' Americans report less caregiving stress and retain a close

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emotional bond with the person with dementia (e.g. Haley et al., 2004). Religion and spirituality are often used to enable coping, both in black American samples and South Asia carers in the UK (Haley et al., 2004; Lawrence et al., 2008). Consideration of the centrality of ethnicity to the impact of dementia on carers, has led Knight and Sayedh (2010) to position this as a fundamental aspect of their sociocultural model of caregiving (see Sociocultural model of caring).

Gender

A further attribute that has a fundamental impact on carers is gender. Although 41% of spousal carers are male (Brown et al., 2007), most adult child carers are daughters or daughters-in-law, and caring is often assumed to be a female role. A review by McDonnell and Ryan (2013) of 56 studies related to men as carers, found that male carers often experienced a sense of isolation. However, many husbands saw their role as an opportunity to repay their partner for the care given to them earlier in life, and many men gained satisfaction from learning new skills and discovering a side of themselves they had not previously developed. Male carers have been found to use a different style of caring from women, using a 'management' or problem-solving approach to make best use of resources. Consistent with this, one review of male experiences of educational support groups found that men preferred terminology such as 'workshops' to 'support groups' (McFarland and Sanders, 2000). Studies suggest that male carers place more value on the informational aspects and skills training, rather than sharing of experiences and emotions.

Young onset dementia

When dementia is of young onset (under 65 years), the carer is usually the spouse, sometimes assisted by children or young people in the family, or if there is no spouse, parents or siblings. The impact for spousal carers is different due to different stage of life of the person and the carer. Since both partners are likely to be of working age, dementia can mean a substantial loss of income with both parties relinquishing work at a time when there may still be considerable household outgoings to pay a mortgage or support young people through their education. Financial advice therefore can be particularly important for families in this position. In addition, any children and young people in the family may have emotional support needs of their own, in addition to the needs of the person with dementia, placing an extra sense of responsibility on the carer at a time when he or she can no longer depend on his or her life partner. Furthermore, as young onset dementia is relatively rare, it may be hard for the carer to meet others in a similar position to break through any sense of isolation. Where young people provide care for their parent, it has been found that this is often invisible if a spouse is seen as the primary carer. Young people may worry about the health of their well parent as well as the parent with dementia, and may feel alienated from their peers, who do not carry similar responsibilities, yet they may not receive services or support in their own right (Allen et al., 2009). This is

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an area where a family approach following diagnosis can be helpful to consider the family's resources and coping strategies and help them to prepare for the future.

A special group among those with young onset dementia are people with Down syndrome, up to a third of whom develop Alzheimer's disease by the age of 55–59 years. Their carers are often ageing parents or siblings who may have supported the person all his or her life. While these carers are often used to caring and know their way around learning disability services, it can be stressful for them to find out that a child, who has already faced adversity due to disability in life, now has to face life with dementia (Foster, 2012). Family carers surveyed indicate that their main concerns are to have full information, to remain fully involved with their relative's care, and to have a chance to meet other carers and other people with dementia (Furniss et al., 2012).

Less common forms of dementia

Finally, carers' experiences are also influenced by the type of dementia. For those dementias that affect language (such as semantic dementia), vision (such as posterior cortical atrophy), social cognition or inhibition (such as behavioural variant frontotemporal dementia, bvFTD), the day-to-day challenges may be quite different from those faced by families where an individual has, for example, memory problems or disorientation. It has been found that carers of people with bvFTD have greater levels of stress and burden than those caring for a relative with Alzheimer's disease (Mioshi et al., 2013). Yet since these dementias are not as common nor as widely known, carers may find themselves lacking information about the meaning of the symptoms and advice about how to best respond. They may benefit from being linked with others through Internet-based groups, overcoming the problems of rarity and distance.

Caregiving over time

Recently there has been an increasing interest in exploring and understanding the 'journey' of caregiving. Within the context of dementia, there are a number of transition points for families and those living with dementia, with each transition representing specific challenges for families, and presenting additional risk of medical errors (Rose & Lopez, 2012). Transitions are defined as 'a passage between two relatively stable periods of time' (Swanson and Tipp-Reimer 1999). Meleis (Meleis et al., 2000; Meleis, 2010) presents the 'Middle Range Theory of Transitions' which provides a useful guide to understanding transitional points for carers and enabling the development of anticipatory interventions to facilitate transitions. Transitions are often triggered by significant events, e.g. when the carer develops health problems, and require new ways of coping and managing. Transitions can be location based, e.g. moving from home to nursing home care, or psychological, e.g. the needs of the person with dementia become more complex.

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Within the context of dementia, carers may experience several different transition points. A number of models and pathways have been proposed which attempt to describe the carer journey. The Global Deterioration Scale (Reisberg et al., 1982) describes transitions in care in terms of the person with dementia's cognitive decline. The scale ranges from 'No subjective complaints of memory' to 'Very severe decline'. Although the scale has some use for describing the transitions in cognitive decline for the person with dementia, it does not explicitly state transition points specific to the carer. More specific to the UK context, the NHS England Transformation framework presents the Well Pathway for families and relatives living with dementia (Department of Health, 2009). The framework outlines and sets the standards for five stages where people with dementia have the right to receive the best care and support. The five stages are: Preventing well, Diagnosing well, Living well, Supporting well, and Dying well. Similar to the Global Deterioration Scale, the Well Pathway does not explicitly describe the carer journey and how to facilitate transitions. This has been found to be the case in a number of countries as described by Fortinsky and Downs (2014), who conducted a review of national dementia strategies within Australia, England, France, Netherlands, Norway, Scotland, and the US. The review found that national dementia strategies tended to focus on transitions in the early part of the journey, and the strategies varied greatly in terms of specific action plans. The strategies were generally focused on preventing or delaying transitions as opposed to facilitating transitions and very few strategies made use of evidence-based approaches to improve the transition process for families. Fortinsky and Downs (2014) proposed six transition points based on their review of national dementia strategies: i) symptom recognition to diagnosis; ii) diagnosis to links with community services; iii) home to hospital and back; iv) home to residential care; v) residential care to hospital; and vi) home or residential care to end-of-life/palliative care.

Although based on the American dementia care context, Rose and Lopez (2012) describe a framework of transitions which is more specific to carers. They outline the following stages at which carers may need more support: the obtaining of the initial diagnosis, advance care planning for financial issues and health care, driving cessation, managing behavioural symptoms, changes in settings (locations), and end-of-life care. Research in the UK by the Carers Trust and University of York (Newbrunner et al., 2013) led to a similar description of the care trajectory in the dementia context. The report 'A Road Less Rocky' describes ten transition points which are termed as 'stress trigger points' for carers. The report highlights the need for timely information and support at each of these ten stress trigger points:

1. when the dementia is diagnosed;
2. when the carer takes on an active caring role;
3. when the capacity of the person with dementia declines;

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4. when the carer needs emotional support and/or a break from caring;
 5. when the person with dementia loses their mobility;
 6. when the person with dementia has other health problems;
 7. when the carer has to cope with behavioural problems;
 8. when the carer's own circumstances change;
 9. when the person with dementia becomes incontinent; and
 10. when decisions about residential and end of life care have to be made.

It is worth noting that all the frameworks emphasize that it is important to note the individual variability within dementia, and therefore not all carers will experience the same transition points in their journey or navigate the points within a specific time frame.

Fortinsky and Downs (2014) note that current dementia strategies focus on preventing transitions as opposed to facilitating carers to navigate through transition points. Recent research has therefore focused on developing interventions to facilitate transitions. A concept that has been particularly useful within this research has been the construct of 'preparedness'. Preparedness has been defined as perceived readiness to assume the role of carer across multiple domains, including meeting the physical and emotional needs of the care recipient and being able to identify relevant services and information (Fujinami et al., 2015). A number of studies have illustrated that low preparedness in caregivers leads to poorer outcomes such as caregiver burden and distress (Fujinami et al., 2015; Yang et al., 2014; Henriksson et al., 2012, 2013; Mak & Sörensen, 2012; Ducharme et al., 2011; Pinquart & Sörensen, 2002). However, most previous preparedness research has been conducted in the fields of cancer and stroke care, and little is known about the impact of preparedness on carers of people with dementia.

Recent research has focused on preparing carers for dementia care, for example a team of Canadian researchers (Ducharme et al., 2011) describe an information intervention designed to facilitate the transition to the point of receiving a formal diagnosis. The research involved 62 carers in the intervention group attending an information programme, with the resulting outcomes being compared to those of 49 carers who did not receive the intervention. The results indicated that the carers who received the intervention were more confident in their role, more prepared, better able to plan for the future, and more likely to use problem-focused coping. The intervention did not have an effect on stress management, perceived support from friends and family, or family conflict. Huang and colleagues (2013) also aimed to improve carer preparedness via a home-based training programme delivered by a registered nurse over two weeks. Unlike Ducharme and colleagues' (2011) study, this intervention was not designed for a specific transition point. The randomized control trial found that the programme improved preparedness, competence, and self-efficacy, but did not have an impact on anxiety or depression. Gonzalez and colleagues (2014) also

aimed to improve preparedness for the care journey through the delivery of six two-hour sessions of resourcefulness training in a group setting. The intervention was tested on 50 carers, with 52 carers in the control group not receiving the intervention. They report that the carers who received the training had higher levels of preparedness and resourcefulness and lower levels of anxiety when compared to the control group. There has been very little research focused on specific transition points in dementia caregiving (with the exception of Ducharme et al., 2011). Further work is required to develop evidence-based interventions to facilitate carer progression through transition points.

Models for understanding caregiving

There are a number of explanatory models or conceptual frameworks, that are used to understand the impact of caring on carers' lives. These are useful because they can lead to an individual formulation of the sources of impact for specific carers, and inform tailored support to address the particular pressure points for different individuals. One fundamental generic caregiving model, which can be useful to keep in mind, was put forward almost 30 years ago by Hall (1990). He proposed that carers are guided by underlying beliefs and values, even though these are not necessarily explicitly articulated or acknowledged. These values come into play alongside the needs of the person with the diagnosis and jointly influence the carer's goals or objectives; for example, the carer's goal could be: 'To care for her, as well as she cared for me' or 'To fulfil my vows by looking after him' or 'To do my best but my children have to come first'. The goals and objectives then influence the carer's practices or acts, i.e. what they actually do in the way of providing care, and these acts are accompanied by emotional responses and feelings. Since living with dementia places many extra demands for support on those around the person with the condition, it is not surprising that stress can result, nor that stress-and-coping theory commonly underpins models used to understand the response of carers to caring. Other models incorporate grief theory, or give greater consideration to positive outcomes or the role of cultural values. In this section, we introduce stress and coping theories in some depth and give a briefer description of other models.

Stress, appraisal, and coping models

The basic tenet of stress and coping theories is that when demands or stressors arise, people use various coping strategies to respond and adapt. Stress arises when the demands that are experienced outstrip the coping resources that a person has available to draw on. Mediating the relationship between demands and stress is the person's appraisal of their situation. In the well-established transactional model of stress, Lazarus and Folkman (1984) proposed two steps of appraisal between stressors and outcomes. Firstly, the person judges whether an event (e.g. the diagnosis of dementia or the development of a new need for support) is relevant to his or her own position. Secondly, the person appraises his

or her own ability to respond effectively, that is to cope, with the perceived threat or challenge. The application of stress and coping theory to dementia care was pioneered by Haley and colleagues (1987) and Pearlin and colleagues (1990), and updated by Sörensen and colleagues (2006) in the light of more recent evidence.

The latter's model is shown in Fig. 54.1, and illustrates four key domains, which are seen as playing a part in determining the outcomes for the carer. These are the background and context, the stressors, and the carer's appraisal of the situation, as well as a number of moderating influences. The background contextual factors include the socio-demographic dimensions of gender, age, ethnicity or culture, and socioeconomic status, all of which set the general scene onto which dementia caring is superimposed. Sörensen et al. divide the stressors into two types: primary and secondary. Primary stressors are those that relate directly to the impact of dementia. As noted earlier, primary stress tends to be more connected with carers' response to behaviour than to cognitive or functional abilities. The secondary stressors include the knock-on effects on other areas of a carer's life, for example, on work or hobbies, finances, or relationships. Dementia frequently challenges the cohesiveness of family relationships. Pearlin and colleagues (1990) proposed that providing care for a relative with dementia could cause family conflict through three routes: i) when there were differences between family members in their beliefs about the nature of dementia and the disability it causes; ii) when there were disagreements about the amount and quality of care required from various family members; and iii) when there was a lack of acknowledgement accorded to the primary carer by other family members. The connections between primary and secondary stressors are seen as being a cascade, as the demands posed by dementia in turn cause other stressors so that there is a proliferation of stress.

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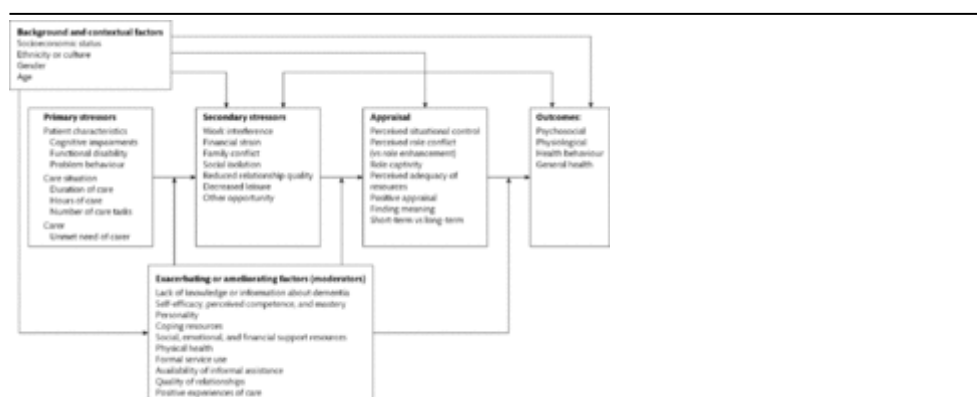


Fig. 54.1

A stress-appraisal-coping model of dementia caregiving.

Reproduced with permission from Sörensen, S., et al. Dementia care: mental health effects, intervention strategies, and clinical implications. *The Lancet Neurology*, 5(11): 961-973. Copyright © 2006 Elsevier Ltd. All rights reserved. DOI:[https://doi.org/10.1016/S1474-4422\(06\)70599-3](https://doi.org/10.1016/S1474-4422(06)70599-3).

The appraisal process draws attention to the way that carers' subjective beliefs about the nature of the stressors and their ability to cope influence their wellbeing. It includes both negative appraisals, such as perceptions of lack of control, role conflict, or role captivity, and positive appraisals, such as finding meaning or having high self-efficacy for caring. Finally, Sörensen and colleagues (2006) include moderators that influence the stress-appraisal process, and these also include factors that can increase or decrease the risk of adverse outcomes. Good levels of information, having available resources, support, or services, and ability to use adaptive coping strategies such as problem-solving may all buffer or attenuate the impact of stress. The outcomes, influenced by these four precursors, are whether the carer experiences physical or mental health problems.

Stress and coping frameworks such as these are quite comprehensive, understandable and clinically relevant. They can provide a useful way of making sense of carers' individual situations and may help to suggest areas for intervention. Some key implications of Sörensen and colleagues' (2006) model are that:

- It is important for clinicians to bear in mind the background variables, which are very significant as they have a strong influence on values, expectations, and resources. It is worthwhile discussing their influence with a carer when establishing his or her response to caring.
- Where there are primary stressors that the carer appraises as a major threat, especially if these relate to behavioural issues, working on how these could be managed can be a valuable focus of intervention.

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- Secondary stressors should be taken seriously as they may push a carer to a point where he or she can no longer tolerate caring. If these arise from family conflict, then problem solving using a family perspective can be helpful.
- Appraisals are powerful. Where these are negative, work to help a person adopt a more positive perspective can make a big difference to the carer's mood. This could be through a cognitive behavioural approach but equally through psychoeducation or through having an opportunity to connect with carer networks that may foster coping and positivity.
- Systematic enquiry about moderating influences may help to identify barriers to coping well, e.g. lack of particular information, that can be addressed.

Sociocultural model of caring

Ethnicity is included as a background variable in Sörensen and colleagues' (2006) stress-appraisal-coping model but is given a more central position in the updated socio-cultural coping and stress model put forward by Knight and Sayegh (2010). They suggest that across all cultures the core of the stress-appraisal process holds true, in that carers experience stressors arising from caring, often perceiving these as burdensome. However, they propose that cultural values influence the resources available to enable coping, through impacting on perceived social support and coping strategies available to carers. For example, in a culture that places a strong emphasis on the obligation to provide care, they propose that the carer may be less likely to perceive others as offering social support; and may be more likely to cope using cognitive coping strategies (for example, positive reappraisal or acceptance) rather than problem-solving strategies. In Fig. 54.2, illustrating their model, they place in bold the three areas that are culturally related and in non-bold the areas they view as being more universal and less culturally determined.

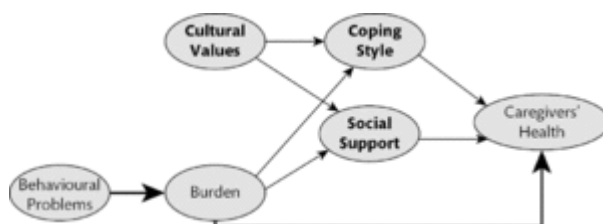


Fig. 54.2
The revised socio-cultural model of caregiving.

Reproduced with permission from Knight, B.G. and Sayegh, P. Cultural values and caregiving: The updated sociocultural stress and coping model. *The Journals of Gerontology: Series B*, 65B(1): 5-13. Copyright © 2009, Oxford University Press. <https://doi.org/10.1093/geronb/gbp096>.

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Loss and grief

In addition to stress-appraisal and coping processes, a further key process in play for many carers, alluded to in the earlier discussion on impact, is the cumulative and ongoing experience of losses which can give rise to mourning and grief. This area has not been as fully explored as the stress process but nonetheless there is research evidence on this area. In one significant study, Ott and colleagues (2007) looked at predictors of grief and personal growth in over 200 carers of people with Alzheimer's type dementia. A small number of factors explained almost 60% and 58%, respectively, of the variance in degree of grief in carers of people with dementia who were living at home or living in care. Where the person was living at home, three variables predicted the degree of grief: i) being unable to achieve a positive state of mind, ii) feelings of depression, and iii) coping by venting distress. For those in care, spouses experienced significantly higher grief than adult offspring. Being unable to achieve a positive state of mind and depression were again associated with levels of grief but coping strategies of self-blame and planning for the future were also significant influences.

Noyes and colleagues (2010) summarize research literature on grief and dementia care, and propose the grief-stress model of caregiving, which adds processes of loss and grief to the stress and coping model. In parallel to overload-related primary stressors, secondary stressors, and stress-related outcomes, they propose a process of loss-related primary stressors that create secondary relationship losses, affecting the sense of closeness and contact with the person cared for. The relationship losses are seen as leading to grief related outcomes such as loneliness, regret, and hopelessness.

Very often in service provision, the stresses associated with caring are more obvious, or more accepted, than the elements related to grief, partly as it may be felt to be taboo to grieve when the individual with dementia is still living, and as the carer may want to protect the person with dementia from realizing the distress she or he is feeling. Nonetheless, it can be helpful for carers to be given space to express their feelings of loss.

A model of the positive aspects of caring

As noted, positive aspects, often referred to as gains or uplifts, are part of the experience for many carers of people with dementia. Carbonneau and colleagues (2010) put forward a conceptual framework for consideration of these aspects. They suggest that, in addition to focusing on the reduction of stressful aspects of caring, psychosocial interventions need to find ways to enhance positive and satisfying aspects of caring. A stress-coping model cannot readily facilitate this and so a means of analysing and understanding the positive aspects becomes necessary. Carbonneau and colleagues based their model on an integrative review of just over 40 research papers. They proposed that the positive aspects of caregiving

are derived from three domains: i) the quality of the daily relationship between carer and cared-for, ii) the meaning of caring to the carer, and iii) the carer's sense of accomplishment from providing care. Whether these positive aspects are experienced are seen as being strongly influenced by both the occurrence of enrichment events in everyday life and the carer's sense of self-efficacy. Carbonneau and colleagues characterize enrichment events as those that leave the carer feeling content, pleased, or joyful. They may arise from a moment of contact, such as a shared joke, or from engaging together in an activity, such as singing in a choir or going for a walk. They may also come from seeing the person with dementia looking relaxed or smiling. It is proposed that such moments of uplift counteract the stresses of caring, but they may dwindle due to the carer lacking the energy, time, and hope needed to bring them about. Here, the carer's self efficacy plays a part, as carers with a stronger sense of self-efficacy who believe that they are capable and can be effective in their caring role, can use this belief to help them set up enriching moments. A recent review of research on the role of self-efficacy beliefs (Crellin et al., 2014) adds evidence to the Carbonneau model, finding across nine studies that higher levels of carer self-efficacy correlated with carer reports of finding meaning, levels of satisfaction and resilience, gain, and positive affect. They noted that carers with high self-efficacy beliefs developed new skills, which in turn led to carers and cared-for enjoying joint activities, that themselves generated positive caregiving experiences (Sanders, 2005; Narayan et al., 2001; Peacock et al., 2010). With the turn to positive psychology, an increasing number of studies are looking at ways to intervene to help carers enhance the gains of caregiving (discussed further on).

Interventions for carers

In preparing this chapter, we asked several carers for their opinions about the most valuable thing that a health professional can do for a carer and that a health professional had done for them (see Box 54.1). They advised that carers should be fully informed and involved in care decisions about their relative; they should be treated with honesty, openness and respect; and carers' needs should be considered as well as those of the person with dementia. All family situations and relationships differ, and it cannot be assumed that all people with dementia wish a close relative to be involved, nor that every person with dementia has a close relative who would want to take on caring. However, given the way that dementia affects the support needs of the person and the impact this then has on the primary carer's life and other family relationships, it is essential for clinicians to consider how to involve whoever is closest to the person with the diagnosis, so that care can be planned and support put in place. Sørensen and colleagues (2006) propose that, when diagnosing dementia, the diagnosing professional should: screen for safety, risk issues, and carer distress; offer acute intervention, dependent on the care dyad's needs, ensuring any intervention is culturally appropriate; provide information and education about dementia and its

management; know how to make appropriate referrals to local or national resources for carers and couples, including support groups, psychoeducational interventions, mental health care for the carer, and case management; and ensure maintenance of gains and review of changing needs over time, as transitions in care arise.

Box 54.1 Responses of family carers to two questions on service provision

The most valuable thing a psychiatrist/psychologist can do for a carer is:

'... to give an accurate diagnosis and explain what that means.' (Barbara Carlton, former carer for her mother).

'... to listen to the carer and also look at things from their view as well as from that of the Service User' (former carer).

'... to look after the carer's mental health as well as the service user' (former carer).

'... listen and try to understand ... not be rude and off-hand about our loved ones. Not force a person with a diagnosis to give things up—try and help us persuade the person it's their choice to stop doing something, for example, driving' (current carer).

'... to be open, honest, and to give relevant, up-to-date information about accessing the various services and help available for both carer and their loved one' (Rachael Norris, carer for her husband).

'... to know I have somebody I can turn to when things get tough.' (Andrea Ryan, carer for her husband).

The most helpful thing that my relative's psychiatrist/psychologist, healthcare team did for me was:

'... to make a diagnosis which meant that I understood what was wrong and then to arrange for a community psychiatric nurse to visit my mother once a month' (Barbara Carlton, former carer for her mother).

'... to include me in all conversations related to the diagnosis, ongoing plans, and strategies available to us' (Rachael Norris, carer for her husband).

'... to help me through changes by explaining things to me and finding ways around them' (Andrea Ryan, carer for her husband).

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'... my father's psychiatrist saw me, recognized me, and valued me to support the lead with my father's care. Her approval validated me' (former carer).

With thanks to TIDE (Together in Dementia Every Day) for the anonymous quotes.

Sörensen and colleagues (2006) identify nine types of intervention that impact on carers. Clustering these by the aspect of the stress-appraisal-coping model through which they impact on carer stress, four intervention types (pharmacotherapy, training for the person with dementia, respite care, psycho-education) aim to reduce the primary stressors of dementia care. Although medication and training for the person with dementia are primarily targeted at the person with dementia, they may have positive knock-on effects for the carer also. A review of pharmacotherapy found that acetylcholinesterase inhibitors provided a small but statistically significant benefit to carers in terms of reducing the hours they spent in caring and their sense of burden (Linger et al., 2005); and a review of training for the person with dementia, for example, through cognitive stimulation therapy, found evidence that active involvement in delivery of therapy for the person with dementia led to significant improvements in carers' quality of life and reductions in carer depression, although there were no changes in caregiver burden or in the quality of the relationship (Leung et al., 2017). Respite care and psychoeducation are principally aimed at removal or reduction of the primary stressors of caregiving, through providing a direct substitute for care that would have been provided by the family carer or by offering carers information and techniques to manage primary stressors more effectively. Psychoeducational interventions are defined as involving the structured presentation of information and techniques to help carers manage the demands of caring. The fifth type of intervention for carers, described by Sörensen and colleagues (2006), is support groups, described as providing a forum to share feelings and concerns and to overcome isolation, and so primarily targeting secondary stressors, such as social isolation. Sixth, are psychological interventions (referred to as psychotherapy). This group of interventions is the only one to overtly focus on appraisals, with the psychological therapies, including cognitive-behavioural therapy, seen as addressing beliefs about dementia and its effects and management. Finally, Sörensen and colleagues' typology includes consultation or case management, multicomponent interventions, and lesser-used interventions (within which they include approaches such as yoga, employer-based interventions, and phone groups).

There is considerable and growing research evidence that respite care and psychosocial interventions can be effective in producing positive outcomes. In their review of 127 studies conducted between 1982 and 2005, Pinquart and Sörensen (2006) concluded that carer interventions

have positive impacts on carer burden and depression, wellbeing, ability, and knowledge, and on the symptoms of the person with dementia. However, while impact is significant, it is also modest and domain specific, highlighting the importance of carefully identifying needs and planning interventions to meet those needs. Needs assessment could be based on a formulation for an individual carer of family around the nine ways in which carers report that dementia impacts on their fulfilment of needs, as described earlier (Pini et al., 2017), or on a systematic consideration of the models of caring.

A meta-analysis by Sörensen and colleagues (2002) considered 87 studies of interventions for carers of people with dementia or elderly relatives with physical health problems. They concluded that day or residential respite care was more effective in reducing subjective burden for carers than psychoeducation or supportive counselling, and respite care and psychoeducation both reduced carer depression and improved carer wellbeing. On the other hand, a review by Maayan and colleagues (2014) concluded that there is insufficient evidence that respite care is an effective approach to management of carer stress. A review of nonpharmacological best practice for family carers of people with dementia (Gallagher-Thompson et al., 2012) concluded that skills training, psychoeducational programmes, individual and family counselling, cognitive behavioural therapies, and multicomponent programmes can all effectively reduce the stress that carers experience. Interventions that are effective have in common that they involve both the person with dementia and the carer, they are flexible enough to be individually tailored and they are intensive or involve active participation (Brodaty et al., 2003; Pinquart and Sörensen, 2006).

Most of the interventions that have been well researched have been designed for use around the time of diagnosis, to assist the person with dementia and carer to be prepared for the future. Brief interventions delivered at this point, for example, six-session skills-training programmes can have positive effects for carers, sustained for up to 32 months afterwards (Selwood et al., 2007). In addition, intensive programmes, such as a 12-day joint residential programme for care dyads, have been found to delay moves of the person with dementia to nursing home care (Brodaty et al., 1997).

One example of an effective short-term intervention that combines psycho-education, skills training for carers, and appraisal-focused work, is the START (STrategies for RelaTives) intervention (Livingston et al., 2013), a UK adaptation of the US-developed Coping with Caregiving programme (Gallagher-Thompson et al., 2003). The UK-based programme consists of an eight-session intervention delivered by non-professionally qualified staff, and accompanied by a manual that carers use to put learning into practice between sessions. The programme covers psychoeducation about dementia; carer stress and sources of emotional support; understanding and managing behaviour of the person with dementia; changing unhelpful thoughts; promoting acceptance; assertive

communication; relaxation; planning for the future; increasing pleasant activities; and maintaining learned skills. Both Coping with Caregiving and START have been found to lead to significant reductions in depression in carers.

An effective supportive intervention is a five-session plus phone support, family-oriented emotional support programme, which is delivered over three months, with the first and fifth sessions of the programme being for the primary carer and the other sessions open to others in the family as identified by the primary carer. The programme has been researched across three countries (US, UK, Australia) with significant reduction in depression in carers being sustained across the two years of follow-up (Mittelman et al., 2008).

Few interventions for carers that focus on later transitions in care have been rigorously evaluated. However, the SHARE (Support, Health, Activities, Resources & Education) intervention (Whitlatch et al., 2015) is an example of an approach designed to enable care dyads to think ahead to some of the difficult situations that may arise as the person diagnosed needs more care. This six-session intervention, developed in the US, involves structured discussions and exercises to facilitate communication between couples about their care values and preferences for future care. A recent randomized controlled trial found that dyads who took part were able to construct a future care plan, and carers experienced improved relationship quality.

As noted, it is important for interventions to be culturally appropriate and some of those described have been tested across ethnic groups with the US (e.g. Coping with Caregiving, Gallagher-Thompson et al., 2003) or across countries. Within the UK, work has been done to adapt and evaluate a carers' programme for South Asian families (Parveen et al., 2017a) but further work needs to be done to develop, adapt, and evaluate interventions to meet the needs of all sections of society, including carers of different ethnicities, sexualities, ages, and carers of those with rare dementias. However, overall, there are many evidence-based ways that health professionals can involve and support carers, treating them as genuine 'experts-by-experience' and as partners in care planning and provision. Interventions that are shown to be effective involve the person with dementia together with the carer, are flexible enough to be individually tailored, and are intensive or involve active participation.

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Elder abuse

Chapter: Elder abuse

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Introduction

From national to local newspapers (see Box 55.1) there are regular accounts of the neglect and abuse of older people, including those with mental health problems. Old age psychiatrists will be readers of such reports; likewise, their patients and their families will see such 'horror stories' fairly regularly. The professional role is evident. Old age psychiatrists may be the first to hear of people's experiences or may learn of incidents from patients' families that cause them concern.

Furthermore, they may be called upon by other concerned professionals, including the police, or their involvement may occur much later when trying to help people survive or cope with a distressing incident or a service to come to terms with an allegation, incident, or scandal.

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Box 55.1 Further reading

'Calls for inquiry over financial abuse of vulnerable care home residents as figures show 13,000 have been affected' (*Telegraph*, 17 February 2018)

<https://www.telegraph.co.uk/news/2018/02/17/calls-inquiry-financial-abuse-vulnerable-care-home-residents/>

'Carer caught on video slapping and abusing dementia sufferer' (*The Independent*, 25 January 2018)

<http://www.independent.co.uk/news/uk/crime/carers-abuse-slaps-dementia-sufferer-video-stacey-george-sabine-marsden-a8177346.html>

'Care worker jailed for abuse of "incredibly vulnerable" elderly people with dementia' (*Eastern Daily Press*, 9 January 2018)

<http://www.edp24.co.uk/news/crime/care-worker-shari-childs-jailed-for-abuse-of-people-with-dementia-at-hillcrest-care-home-1-5346926>

'Phone scam gang who stole 16 Hull pensioners' life-savings jailed for 33 years' (*Hull Daily Mail*, 1 December 2017)

<https://www.hulldailymail.co.uk/news/hull-east-yorkshire-news/phone-scam-gang-who-stole-864198>

The chapter describes some of the challenges that confront old age psychiatrists working within contexts where abuse and neglect of older people are of rising concern. This chapter *could* focus entirely on definitions, quantifying the nature of the problems, or risks, but knowledge here is still partial. While presenting some discussion of these matters, the chapter also draws attention to practice responses and interventions that appear to have some success in reducing risks and minimizing harms. The chapter also points to new areas of concern beyond interpersonal violence that are beginning to threaten the wellbeing of vulnerable older people, particularly online threats. It is important to note that, while some mental health problems such as depression may be a risk of heightened vulnerability, there is room to explore if depression is linked in other ways to victimization, or is a response to it. Old age psychiatrists could assist researchers in exploring the links between expressions of distress and elder abuse to promote survival and resilience among older people. They could also assist in the development of interventions to treat perpetrators for whom there is currently little help and about whom we have little understanding.

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Defining elder abuse

It is no exaggeration to say that definitional variations plague the subject of elder abuse and adult abuse generally (Dixon et al., 2009). As yet there is no universally accepted definition of elder abuse, but the following is often used:

A single or repeated act or lack of appropriate action occurring within any relationship where there is an expectation of trust, which causes harm or distress to an older person or violates their human and civil rights (World Health Organization, 2002).

There is general unanimity that elder abuse, of whatever type, may result in serious adverse consequences for older people but increasingly it is merged with infringements of dignity or of other human rights where harm is less easy to quantify and often more subjective. A recent systematic review concluded that elder abuse may affect one in six older people worldwide, approximately 141 million people (Yon et al., 2017). Evidence from most low-income and middle-income countries is also growing; see studies from India (Chokkanathan et al., 2013; Evandrou et al., 2017) and Malaysia (Sooryanarayana et al., 2017).

Less commonly referred to are instances where older people are the 'perpetrators' of abuse and neglect. This is a group about which we know very little; indeed, studies of 'perpetrators' in this area are few. One feature of elder abuse has been its relative isolation from other research and practice debates, including, until recently, domestic violence and 'hate' crimes. Researchers in the US have commented that a better understanding of domestic violence may help in understanding, and then addressing, the reluctance and often refusal of older victims to take action or to accept protective services (Jackson and Hafemeister, 2012).

Generally, elder abuse is a term used to refer to the ill-treatment of an older person (usually defined as over age 65 years) by commission or omission. Terms such as maltreatment or mistreatment are also commonly used. Abuse may occur both in home or domestic settings (the older person's own home, a relative's home, or supported or sheltered housing) and in other settings (day-care centres, sheltered or assisted living facilities, care homes (residential and nursing), and hospitals). Some kinds of behaviour definable as abuse are criminal acts, such as assault and theft, or wilful neglect of a person lacking mental capacity (in England and Wales). There are other actions or behaviours that may be more contingent upon particular circumstances, such as restraint. More commonly, classifications centre round psychological abuse (bullying, shouting, or swearing), physical abuse (hitting, shaking), sexual abuse, financial abuse, and medication or institutional abuse. In addition, people may experience several types of abuse; an Irish study (Clancy et al., 2011) found that the most frequent combination was psychological and financial abuse (20% of all reports). There have been claims that physicians consistently underestimate the prevalence of elder abuse

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(Cooper et al., 2008), and while general estimates of around 5% of the older population may be a reasonable conclusion; this may be much higher among people with mental health problems. However, Gilhooly and colleagues (2016, p. 9) have reported that professionals are more likely to decide that financial abuse is definitely taking place, and are more likely to act if the victim is 'mentally incapacitated'.

Definitions are important—they not only determine who will be counted as abused and who will not, but they also affect the legitimate interventions by professionals and the powers of the criminal justice and regulatory sectors to intervene in family life, in care and health activities or businesses, and everyday transactions. Governments have also given powers to older people to hold other people to account if they abuse or neglect them. Recourse to action may be by complaint or by authorizing others to act on their behalf; old age psychiatrists need to be aware of such systems.

Financial abuse is one area where these definitions and risks are controversial and this may be expressed in calls for professional assistance or action. At one level it can be seen as a crime and sheer exploitation. Gilhooly and colleagues (2016) have classified possible motivations:

- Malicious—deliberately not spending assets for the wellbeing of the donor to protect an inheritance
- Malicious—deliberately spending or taking assets for their own personal benefit
- Opportunistic—a spur of the moment, unplanned act
- Misplaced moral justification—believing the victim would have wanted them to use the assets for their own benefit
- Neglect
- Incompetence

There is increasing concern about the targeting of older people or vulnerable adults from afar (email and telephone scams), as well as sophisticated and aggressive door-to-door theft, deception, exploitation, and repeat victimization (Alzheimer's Society 2011; Manthorpe et al., 2012). Oliver and colleagues (2016) have recently outlined the vulnerability of some older people to mass marketing fraud and the techniques used to entrap them.

In most developed states, policies and procedures outline the expected response of national and local government to incidents and allegations of elder abuse (see, for example, Sethi et al., 2011). In England, the term safeguarding describes multi-agency arrangements to prevent and respond to the abuse of vulnerable adults. This term was adopted to mark a shift in emphasis from reaction and rescue to prevention and harm minimization, in the hope that outcomes for the older person might be

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better and of their own choosing. English law was recently updated, and the Care Act 2014 clarifies the responsibilities of professionals and organizations and prompt more consistent responses. Local authorities must lead a multi-agency local adult safeguarding system (including the NHS) to prevent or stop adult abuse and neglect. They are required to make 'enquiries', or ask others to do so, when they think an adult with care and support needs may be at risk of abuse or neglect. Furthermore, they need to determine what action may be needed and acceptable to safeguard the person. In each area they must set up a Safeguarding Adults Board (Board) that includes representatives from both the NHS and the police and create a joint safeguarding strategy. The Board must undertake a Safeguarding Adults Review when someone with care and support needs dies as a result of neglect or abuse and there is a concern that the local authority or its partners could have done more to protect them. Finally, the local authority must arrange for an independent advocate to represent and support someone who is the focus of a safeguarding enquiry or review, if required. The implications for professionals such as psychiatrists are clear—starting with their responsibility to raise concerns or to prompt an enquiry; to offer advice about a person's ability to make decisions or give evidence, to take part in planning for support, and to cooperate with any Safeguarding Adult Review. In some instances, they may be asked to provide specialist or expert opinions or to support colleagues. While there is not mandatory reporting in the UK, professionals must abide by their codes of conduct, and may need to break confidentiality.

How much elder abuse is there?

For many years, researchers maintained that abuse of older men and women was not a rare phenomenon and that societal action was not required. Wilson (1994) argued that high rates of elder abuse and neglect existed among elderly mentally ill (EMI) clients of health and social services. She concluded that EMI services might expect abuse rates of 30–50% among users. Other studies have asked family carers about their behaviour where it may be hard to ask older people directly and where carer emotions and behaviour are a focus of professional activity. For example, Cooper and colleagues (2010) undertook longitudinal research among family carers of people with dementia who had been referred to community mental health teams. As many as half of these carers admitted abusive behaviour at baseline:

The psychological abuse items asked were whether they had: screamed or shouted at the care recipients, used a harsh tone of voice, insulted, swore at them or called them names; threatened to send them to a care home, to stop taking care of or abandoning them; or used physical force on them. The physical abuse items were: whether they had been afraid they might hit or hurt them, whether they had withheld food, hit or slapped, shaken or handled them roughly in other ways (Cooper et al., 2010, p. 482).

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The proportion of family carers who reported such behaviours had not only increased to nearly two-thirds one year on, but also this had persisted or worsened, despite carers' use of specialist mental health and other services (and their use by their relatives). The researchers concluded that targeted therapeutic interventions were needed to change carer abusive behaviour, particularly focused on reducing carers' depression and anxiety.

Who is at risk?

Patterson and Malley-Morrison (2006) have maintained that older people are universally susceptible to abuse, explicable by several individual and social, or ecological, factors. Community-based studies that surveyed large representative groups alerted professionals to potential hazardous situations, 'risky people', and client frailty. For example, the UK National Elder Abuse Study (O'Keefe et al., 2007) pointed to the risks faced by disabled older people being cared for by their partners. They concluded that this situation might lead unintentionally to poor-quality care and neglect as these family carers found their responsibilities increasingly difficult and when they perceived, rightly or wrongly, that services were inaccessible or inappropriate. Biggs and colleagues (2010), undertaking further analysis of this UK survey (which did not include people living in care homes or who used proxies for those unable to participate), found that the ways in which risk factors affected the likelihood of reported mistreatment and neglect were varied and complex. They concluded that a risk factor could have a causal influence, be the result of mistreatment, abuse or neglect, or some other factor might be more influential. Using the example of depression, which emerged as one of the risk factors associated with mistreatment (regardless of definition used), they found that, although depression may increase the likelihood that older people perceive and report mistreatment, it may also be a consequence of experiencing mistreatment or indeed a response to some common factor, such as mobility problems.

There is not great evidence that particular individuals are more at risk than others. Claims are made about some factors (gender, socioeconomic status, location, and so on). Not surprisingly, professionals working in different areas often conclude, with the apparent support of associated researchers, that their clients are at greater risk than others. There is some evidence that older people with cognitive impairment are at greater risk than other older people (Choi et al., 1999; Alzheimer's Society, 2011) but it may be that they are more likely to be referred for interventions. The Chicago Health and Aging Project (CHAP) (Dong et al., 2011) found an increased risk of reports of elder abuse to a social services agency among older people (aged 65 years and over) who had lower levels of global cognitive function, lower scores on the Mini-Mental State Examination (MMSE), and reduced episodic memory and perceptual speed. They recommended that relevant health professionals should screen for elder abuse alongside the cognitive screening and that 'red flags' for potential elder abuse 'should be raised for vulnerable,

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cognitively impaired individuals, especially those without the support needed to meet their most basic day-to-day needs' (p. 214). They further advised more discussion of elder abuse and dementia among and between relevant agencies.

It is now generally accepted that elder abuse affects or potentially affects a wide variety of older people. Moreover, what might be protective might be hazardous (e.g. living with family members or being in a care home, may protect or evoke new risks). The use of terms such as 'place of safety' is now generally avoided since no location or relationship has emerged as beyond reproach.

Prevention

While there may need to be a dual focus on prevention and response when addressing the abuse and neglect of older people with mental health problems in settings of all types, examples of prevention have not greatly been researched and so the evidence base for practice is thin. Nonetheless, old age psychiatrists need to be aware of local systems and resources that may assist with primary prevention—services which enable older people to seek help with worrying family relationships, or enable them to raise concerns about care workers or 'false friends' in person and remotely (promising romance, or lottery windfalls). Such opportunities for informal advice or counselling may be found in community, faith, and voluntary sectors, and part of prevention lies in informing social networks that there is help available, but also that they have a role in reducing loneliness and tackling feelings that nothing can be done. The fear and shame associated with admissions of elder abuse or even suggestions that independence is threatened need to be considered. As with primary care professionals, if approached by individual older people about their distress or fear, old age psychiatrists need to listen carefully to what is being said or what is *not* being said. The views of other members of the multidisciplinary team can provide different insights into family or care settings. Somatic complaints or expressions of anxiety, depression, apathy, and distress may be symptoms that suggest matters are slipping out of control and that previous coping strategies are inadequate. The situation of older parents supporting an adult child with addiction problems is often seen as an example where, to some professionals, the parent may be a resource, but to other professionals the older person may be at risk of exploitation since their ability to call for help may be undermined by their loyalty to their child.

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Further work on strategies to prevent abuse would be timely because many public educational initiatives may not be easy for older people with dementia (and many others) to comprehend or recall. Other multidimensional approaches that are part of public policy in the UK and contribute to prevention of abuse include:

- Setting up requirements for checks of care workers and volunteers to see if they have a criminal record that might lead a person not to take the risk of employing them (UK);
- Establishing a 'vetting and barring' list of people who must not be employed to work with vulnerable adults and criminalizing an employer if they do employ any person who is barred (England);
- Criminalizing the wilful neglect or ill-treatment of people who do not have mental capacity (Mental Capacity Act (MCA) 2005) (England and Wales);
- Amending sexual offences law to criminalize the sexual abuse of vulnerable adults;
- Setting up higher expectations that staff will be trained to support vulnerable adults;
- Learning from inquiries or reviews of professional or system failures (Manthorpe and Martineau 2016).

Internationally, a recent systematic review concluded that the most effective place to intervene to prevent elder abuse would be to focus on reducing physical restraint by long-term care workers (Ayalon et al., 2016). Old age psychiatrists may be able to play their part in such initiatives. Their roles in leadership and team work when responding to 'incidents' or encouraging preventive measures have not been much researched but their expertise may be useful in avoiding scapegoating, blame, and loss of morale. More proactively, they could model behaviour that encourages the voicing of concerns and supports staff who are facing ethical difficulties.

Preventive measures that can be recommended by old age psychiatrists include giving information to older people about the potential to plan in advance of loss of decision-making capacity, whether this is temporary or permanent. Such information may be useful to people newly diagnosed with dementia as it enables them to consider their options and ways in which they can protect themselves from abuse to some degree. Practitioners' roles can encompass providing information about advance care and financial planning, what to do when decision-making capacity is declining as well as absent; helping family members and the wider care team assess decision-making capacity; recommending specific support services and expertise to people with dementia and carers; and referring them to sources of help (Widera et al., 2011). For older people with fluctuating mental health problems, being able to set out their choices

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about care and treatment that can be taken account of if they are in great distress is a further matter that professionals can discuss.

One key point that has exercised professionals working with people who are able to make their own decisions is that of patient confidentiality. Old age psychiatrists are likely to have to advise team members on such matters, and should be aware of local policies and their responsibilities. Practitioners, of course, do not generally share information with other agencies or take action without the consent of a person who has the capacity to make this specific decision where there is no overriding duty above the normal duty of patient confidentiality. However, in England, such a duty may apply when someone else without mental capacity is at risk (e.g. another member of the family or another resident in the day centre might be at risk from a malevolent volunteer or care worker) where a 'safeguarding adults' referral should be made about that person. The duty also applies when someone publicly employed in a position of trust is apparently responsible for neglect or abuse.

Action and response

This chapter identifies that elder abuse may be unreported, undetected, and underestimated by professionals overall and suggests that old age psychiatrists have particular roles in supporting older people at risk of such harm (including perpetrators) and as leaders of services and teams. What can be done? This chapter concludes by exploring three areas illustratively.

First, there is some evidence that educational interventions with practitioners can be effective. Cooper and colleagues (2012) reported on an educational elder abuse intervention and its impact on practice. Forty trainee psychiatrists in two London National Health Service (NHS) Trusts completed the KAMA (Knowledge and Management of Elder Abuse) and the CSQ (Caregiver Scenario Questionnaire) to measure their knowledge about managing and detecting elder abuse, before and immediately after a brief group education session. The researchers asked how often participants considered, asked about, detected, and managed cases of possible elder abuse. They measured the psychiatrists' confidence in doing so, at baseline and three months post-intervention. Immediately post-intervention, the participants scored significantly higher on knowledge, compared with baseline, and identified more items that were either definitely or possibly abusive. At three-month follow up, 24 (60%) participants reported higher confidence in managing abuse and considered it more frequently, but despite this they indicated that they did not ask older people and their carers about abuse more frequently. There was no significant change in detection of abuse cases compared with a three-month period before the intervention (Cooper et al., 2012).

The researchers concluded that the value of this brief educational intervention lay in the increase of the trainee psychiatrists' knowledge and greater vigilance for abuse immediately and after three months.

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However, the trainees still remained reluctant to ask patients about abuse, citing reasons such as fear of causing offence or harming the therapeutic relationship, as well as being unsure how to ask people with dementia about the subject. The researchers suggested that changing professional behaviour may require a more complex intervention than education alone, and recommend that this is devoted to improving communication skills. This may be equally applicable to other professionals.

Second, at policy level, measures to enhance self-efficacy and learned resourcefulness could be promoted by old age psychiatrists to increase resilience among older people, possibly working more collaboratively with domestic violence organizations that offer refuge and rebuilding of confidence, but also working with perpetrators and with survivors' networks. Action on elder abuse means addressing social isolation as well as enhancing existing social networks. The multiple risk factors of isolation and loneliness are found in many studies of elder abuse, and appear applicable to stressed carers and some perpetrators, as well as victims of abuse. It is well recognized that older people are easily isolated as a group from public policy strategies unless specifically identified. A simple focus on abuse neglects other aspects of social connectedness.

Lastly, as a result of media reports there may be urgent work to do in persuading families and older people that not all care providers are characterized by poor or abusive practice. Otherwise people may choose not to seek early support. One area where old age psychiatrists may be able to offer meaningful reassurance is by explaining to relatives that their patients living in care homes are still entitled to NHS services and they should be able to outline how residents and care home staff are still able to access their support when needed.

Care workers are often unfairly described as under-skilled and lacking training and their work is seen as low status, poorly paid, and difficult (Hussein and Manthorpe, 2012). Effective support from health services is crucial for care homes. Gordon and colleagues (2018) found that working between healthcare services and care home staff was enhanced by: i) investment in care home-specific work; ii) relational working which over time builds trust between practitioners; iii) care which 'wraps around' care homes; and iv) access to specialist care for older people with dementia. Under these circumstances, there are likely to be positive outcomes in terms of reduced hospital admissions and overall care. These strong relationships may also have an important part to play in preventing abuse and neglect.

Conclusion

Older people with mental health problems often have great strengths and resilience, but their frailty may place them at increased risk of harm from others. As with other facets of their care and treatment, minimizing undesirable risks is an ongoing process and requires good partnership

working between health and social care, between formal and informal networks, and may involve experts from other areas, in prevention, befriending, evidence collecting, care coordination, and monitoring. This chapter has outlined aspects of the risks of elder abuse affecting older people. There is international interest in how to manage the tightrope of over- and under-protection and a sharper focus on interventions that limit perpetrators' ability to exploit or harm older people. Other interests include searches for effective and acceptable interventions. The prevention of abuse, the minimization of harm, and the provision of effective responses all require good working relationships, record keeping, analysis, observation, and listening skills, as well as being able to 'think the unthinkable'. These skills can be fostered among local services and communities by old age psychiatrists.

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Older people as victims and perpetrators of crime

Chapter: Older people as victims and perpetrators of crime

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Older people as victims

Crime against ageing individuals is recognized as a worldwide phenomenon, which transcends cultural values and societal attitudes (Ryan, 2009). It is predicted that by 2050 the global population of individuals over 60 years old will reach two billion, from the current 900 million (WHO, 2017). At the current prevalence rates, 320 million older people will be the victims of crime (WHO, 2017). A large proportion of these will be located in low- and middle-income countries, where resources to deal with these issues are often inadequate (WHO, 2017).

This section of the chapter focuses on older people as victims. We do not want to restrict our discussion solely to those actions that are identified as crime as these constitute only a small part of all the types of harmful acts against older people, such as abuse, which are not necessarily detected and pursued through the criminal justice system. This section is in three parts. The first focuses on older people as victims of actions that

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are regarded as crime; the second on abuse of older people, which may not necessarily be reported as crime. The final section reports on issues of identification, reporting, prevention, and intervention, which apply to all types of victimization of older people.

Older people as victims of crime

This section focuses on the existing evidence around criminal acts against older people by reporting on criminological data and by making comparisons with offences against younger victims. It also discusses data regarding violence in residential and institutional care settings. Most research data concern violent crimes (i.e. murder, robbery, and assault), sexual violence, and financial fraud.

Violent crime

Statistics show that violent crime perpetrated against older individuals, aged 50 years old or above, occurs 20 times less frequently than violent crime against younger people (Bachman and Meloy, 2008). However, this may be a considerable underestimate, given that prevalence data rely on police reports and adult protection services, and these crimes may often be undisclosed to the authorities (Bachman et al., 1998). However, it may also be the case that older people make fewer interactions outside their home and are therefore less at risk of some types of violence. Despite the lower rates of falling victim to violent crime, it should be noted that older people may be disproportionately fearful of such crimes and, if they are attacked, may find it more difficult to recover from the incident than younger people.

The risk of being murdered is lower among older people than at any age and its incidence has remained stable in the last few years (Klaus, 2005). Compared to violence against younger victims, there are differences in relation to the method and context of killing, as well as the perpetrators' characteristics. In the UK, while the prevalence of murder among the over 50s is similar to that in younger people, there are some gender differences. In 2015, 13% of female victims of homicide were aged 75 and over, 9% of the UK female population being in this age group. Conversely, 4% of male victims were over 75 years old, 7% of the UK male population being in this age group (ONS, 2016). Older victims are more frequently killed during robbery, while younger ones more often following interpersonal conflicts (Bachman and Meloy, 2008). While overall homicide statistics report that perpetrators are more likely to be known to the victim, for elder homicide strangers account for a large proportion of the perpetrators (Bachman and Meloy, 2008).

As with homicide, the risk of falling victim of robbery decreases with age (Bachman and Meloy, 2008), except for street robbery and handbag snatching (Klaus, 2005). While younger victims of robbery are more likely to be male, victims in the older group are equally shared in terms of gender (Bachman et al., 1998).

Older people as victims and perpetrators of crime

The prevalence of assault is lower for older victims compared to younger ones (Klaus, 2005). The victims more frequently know the perpetrators, who often are their spouse or a family member (Bachman and Meloy, 2008). Therefore, compared to assault against younger victims, elder assault is more likely to occur at home than in public places (Bachman and Meloy, 2008).

The physical consequences of falling victim of violent crime can be particularly serious for older individuals, especially if they are frail. Several studies on older female victims have reported that they more frequently require medical attention for physical injuries, in comparison with younger female victims (Bachman et al., 1998; Bachman et al., 2004). Research also confirms that the risk of death following assault is higher among older victims than among younger ones (Chu and Kraus, 2004).

The evidence relating to violent crime in care homes and institutional settings is very limited, particularly around resident-to-resident violence, which remains the most common type of violence in these settings (Lachs et al., 2007). In terms of staff-to-resident violence, research studies tend to include violent acts within the overall category of elder abuse, which also includes emotional and psychological abuse, making it difficult to derive specific data for violence (Bachman and Meloy, 2008). Moreover, the few studies available are based on reports of members of staff, which limits the accuracy of reporting, given their conflict of interest in reporting malpractice. In one US study (Pillemer and Hudson, 1993), 17% of the nursing staff admitted to having used excessive physical restraint against residents and 10% to having pushed, grabbed, or shoved a resident in the last month. However, in another US sample of nurses working in home facilities, only 3% admitted to having used any type of violence in the last year (Pillemer and Bachman, 1991).

Several risk factors for staff-to-resident violence have been identified. They include: residents' characteristics (dementia and high-dependency needs) (Talerico et al., 2002; National Center on Elder Abuse, 2000, 2005); staff characteristics (young age, poor education, little experience of work with older residents) (Pillemer and Bachman, 1991; Pillemer and Moore, 1990); staffing issues (inadequate training, low staffing, high turnover, work-related stress, and 'burn-out' (National Center on Elder Abuse, 2000), (Pillemer and Bachman, 1991; Pillemer and Moore, 1990; Shaw, 1998); and infrastructural issues (i.e. accessibility issues) (National Center of Elder Abuse, 2000).

Sexual violence

There is no consensus across different jurisdictions on what constitutes sexual violence, and in some instances the term sexual abuse is used interchangeably. Sexual violence can encompass actions perpetrated by individuals known or unknown to the victim (Johannesen and LoGiudice, 2013). The matter is further complicated by the fact that for sexual

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offences, unlike for other offences, the issue of consent is central to determining whether an offence has been committed or not. Therefore, the same action could either be consensual sex or rape. In the case of older people, their ability to consent may be affected by mental disorders and cognitive decline to a larger extent than in younger individuals. Therefore, it may well be that what was previously consensual sex with a long-term partner is later technically a crime, as one of the two partners has lost their capacity to consent. Such issues pose significant challenges to providers of services for older people, who have to strike a balance between protecting individuals from unwanted sexual activities while not depriving them of pleasurable activities in the context of a loving relationship. Here, we only present data around sexual violence.

Contrary common assumptions, research evidence suggests that the risk of sexual victimization does not decrease with age, particularly among women (European Union Agency for Fundamental Rights, 2014; Mann et al., 2014; Stockl et al., 2012). The prevalence of self-reported elder sexual violence ranges between 0.2% (O’Keeffe et al., 2007) and 17% (Lisboa et al., 2009). Risk factors include being a woman of white ethnicity (though this perhaps reflects the likelihood of reporting rather than a true increase in prevalence), being aged between 60 and 70 years old (Baker et al., 2009; Ball and Fowler, 2008; Bows and Westmarland, 2017; Jeary, 2005; Lea et al., 2011; Naughton et al., 2010; O’Keeffe et al., 2007), having poor physical and psychological health, cognitive impairment (i.e. intellectual disability, dementia), and poor communication skills (Pinto et al., 2014). As with homicide, elder sexual assault most often occurs in the victim’s home and in care homes/institutional settings, rather than in public places (Ball and Fowler, 2008; Jeary, 2005; Teaster et al., 2001).

Perpetrators tend to be male, often much younger than the victim, and with previous convictions (Bows, 2017). Research has also evidenced that, in contrast with younger victims, sexual violence committed by strangers is more common (Bows, 2017). In care homes and institutional settings, while some studies have found that members of staff are the most likely perpetrators (Baker et al., 2009), others have reported that peer-to-peer sexual violence is more common (Roberto and Teaster, 2005).

The impact of sexual assaults on older victims can be both physical and emotional. While the risk of HIV and other sexually transmitted diseases is in line with younger female victims of sexual assault (Sormanti and Shibusawa, 2008; Sormanti et al., 2004), older victims are more likely to experience genital trauma (Jones et al., 2009; Morgan et al., 2011; Muram et al., 1992; Ramin, 1997; Templeton, 2005). High mortality rates have also been reported, with over half of the sexually assaulted older women dying within one year (Burgess et al., 2000). As in younger victims, emotional consequences of sexual violence include low self-esteem, hopelessness, numbness, social withdrawal, sleeping problems,

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flashbacks, and nightmares, though these effects might be more severe in older people (Burgess, 2006; Jeary, 2005).

Financial fraud

A necessary distinction is to be made between financial abuse and financial fraud, the first being perpetrated by people known to the victim, the latter not necessarily occurring in the context of victim-perpetrator acquaintance. Financial fraud includes doorstep crime (selling goods or services at extortionate prices), bank account theft, mass marketing fraud (e.g. asking for upfront payment for goods or services), pension fraud, investment fraud, and cybercrime (Age UK, 2015). These crimes may be perpetrated through the web, mail, phone, and texts (Age UK, 2015), through various expedients, such as befriending or coercing the victim, using false credentials or credible documentation (Button, Lewis, and Tapley, 2009), selling dreams at a low price, and taking relatively small amounts of money (Age UK, 2015). The victims are often included in 'sucker lists', making them susceptible to further victimization (Age UK, 2015).

Prevalence studies report high prevalences of financial fraud of older people: 53% of people over 65 years old believe they have been the victim of this crime and 70% of those responding to the financial requests of scammers have lost money. This percentage amounts to 500,000 people in the UK alone (Age UK, 2015). Older people are much more likely to be targeted than younger people, as more than half the cases of financial fraud are perpetrated against people over 55 years old, who also experience twofold financial losses, the mean loss per scam being £684 for victims below 55 years old, and £1,261 for those aged above 55 (Age UK, 2015).

The most common type of financial fraud among older people is doorstep crime, with 85% of the victims above 65 years old being a victim of this type of crime (Andrews, 2014). The victims are more likely to live alone (62%) and have a physical impairment (63%) (Andrews, 2014). Social isolation (40%), depression in the last six months (36%), and bereavement in the past two years (33%) are also common, and cognitive impairment is present in 14% of the older victims (Andrews, 2014).

As for other types of crimes, prevalence estimates of elder financial fraud may be conservative, as the phenomenon may be largely underreported due to several factors, including a sense of shame on the part of the victims (Age UK, 2015). Risk factors include social isolation and cognitive impairment, as well as victims' overconfidence in their capability to make financial investments (Lea et al., 2009).

The impact of financial fraud is both practical and psychological. Financial losses can take a higher toll on older people, who may have to live on limited fixed income. Research has identified that 46% of older victims experience financial difficulties (Andrews, 2014). Deteriorating

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psychological health is also common among the victims of financial fraud, who may be exposed to stress, anger, and loss of self-esteem (Age UK, 2015). 40% of victims report a sense of shame and 28% symptoms of depression (Andrews, 2014).

Older people as victims of abuse

Abuse or acquaintance violence is defined as 'a single or repeated act, or lack of appropriate action, occurring within any relationship, where there is an expectation of trust which causes harm or distress to an older person' (Wood et al., 2010). Abuse can be intentional, but sometimes the perpetrator may be unaware of the harm being caused to the older person (Wood et al., 2010). Either way, the concept of abuse implies an existing relationship between the perpetrator and the victim.

While abuse against children and women has been the focus of research, policy, and prevention/intervention strategies since the 1960s (Kleinschmidt, 1997), elder abuse was neglected until the mid-1970s, when the phenomenon was first identified as 'granny battering' (Baker, 1975; Burston, 1975). Since then, the understanding of elder abuse, how it is perpetrated, experienced, prevented, and dealt with has grown. This development notwithstanding, abuse of older people has not yet been comprehensively addressed in international health policy documents (Yon et al., 2017). The recently established 17 Sustainable Development Goals of the United Nations mention abuse against women (target 5.2) and children (target 16.2), but there is no reference to abuse against older people (United Nations, 2017). In addition, progress has been hindered by governmental underfunding of campaigns, programmes, and interventions. In 2009, in the US, the annual spending for all activities related to elder abuse was \$11.9 million, compared with \$649 million for women and \$7 billion for children (Dong, 2015). To raise awareness among policy makers, professionals, and the public, the International Network for the Prevention of Elder Abuse (INPEA) designated 15 June as World Elder Abuse Awareness day for the first time in 2006, ratified by the United Nations in 2010 (United Nations, 2013).

Elder abuse includes:

- Physical abuse, causing physical harm, pain or injury, through restraining, hitting, grabbing, pushing, slapping, and bruising the older person (Wyandt, 2004).
- Psychological or verbal abuse, which may cause emotional harm or pain to the older person through humiliation, insults, infantilization, yelling, and threats (Wyandt, 2004; Kleinschmidt, 1997).
- Sexual abuse, engaging in any non-consensual sexual act with an older person.
- Financial abuse, the illegal or improper exploitation or use of funds or other resources of the older person (WHO, 2002), which may include misappropriation or mismanagement of financial assets,

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account takeover, investment fraud, pension fraud, and inheritance fraud (Age UK, 2015).

- Neglect, failing to fulfil the care needs of the older person or provide assistance in activities of daily living (Kleinschmidt, 1997).

A culture-sensitive approach to considering these five categories is crucial, as marked variations exist across cultures as to what constitutes elder abuse (Pillemer et al., 2016). Caution is required when comparing prevalence data across different countries too. Sooryanarayana and colleagues (2013) found that prevalence rates in high-income countries are higher than those reported in low-income countries, due to the cultural variations on how the phenomenon is perceived and reported (Kleinschmidt, 1997). As an example, in parts of India and Africa it is customary that widows are forced into finding a new husband, they may be banished and their financial assets (e.g. property) may be seized by family members (Kumari, 2014; McFerson, 2013). While this would be classed as abuse in other countries, it is unlikely to be reported as such in countries where such behaviour is the cultural norm.

How elder abuse is defined also depends on different concepts of who is regarded an 'older person'. Some countries, such as Ireland, consider a retired individual over the age of 65 to be 'older', while others use 60 years old as criterion for inclusion in the older age category (Ryan, 2009). In Australia, Aborigines are considered older at age 50 (Wainer et al., 2010) and the cut-off is as low as 45 years old for indigenous women, given their lower life expectancy (McFerran, 2008).

The perception of elder abuse also varies with age and gender. Young people tend to identify abuse only in more serious cases, while older people are more likely to acknowledge the subtleties of emotional abuse (Daskalopoulos et al., 2007; Childs et al., 2000). In addition, a UK study found that women are more knowledgeable of elder abuse and aware of its extent, compared to men (Hussein et al., 2007).

How serious the abusive behaviour is perceived to be also depends on the victim's characteristics. In those not considered of 'sound mind', such as in dementia or in the presence of other mental health issues, the abuse may be less likely to be acknowledged by others (Werner et al., 2006; Mills et al., 1998).

Prevalence of elder abuse

A recent review by Yon and colleagues (2017), based on 52 studies in 28 countries, presents the most up to date pooled prevalence data on elder abuse. The authors report a 15.7% prevalence for 'any form of abuse', equal to one in six (141 million) older adults worldwide.

In relation to single countries, in the UK, 2.6% of older people aged 66 and above residing in private accommodation report any type of abuse on the part of family, friends, or caregivers each year (Biggs et al., 2009). In

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the US, 10% of respondents to a phone survey reported being abused (Peterson et al., 2014; Burnes et al., 2015). A similar prevalence (9%) was found in a population-based nationally representative study in the US involving 3,000 community-residing participants aged 57–85 (Laumann et al., 2008). Prevalence data range from 1% to 4% in Australia; in Norway, Finland, and the Netherlands the estimate is around 5%, in Sweden and France 17% and 20% respectively (Fallon, 2006), and in Spain over 40% (Sooryanarayana et al., 2013).

High prevalence is also found in some Asian countries, where a review synthesizing results from 18 studies, using one-year prevalence rates, found that India had a higher aggregate rate for all types of abuse (14%), compared to Europe (6%) and Canada (4%) (Pillemer et al., 2016). The marked differences across countries can be explained by the lack of standardized tests to detect abuse, with a range of assessments and methods employed in the existing literature, paired with different age cut-offs for inclusion in the older age category (Sooryanarayana et al., 2013).

In relation to specific types of abuse, Cooper and colleagues (2008) found that one in four older people experienced significant levels of psychological abuse, which was identified as the most prevalent type of abuse. This was followed by neglect, financial abuse, and physical abuse. The least reported form of abuse was sexual abuse, with prevalence varying from 0.04% in Nigeria (Pillemer et al., 2016) to 1.3% in Spain (Sooryanarayana et al., 2013). It is relevant to note, however, that these data probably underestimate the problem, as identification and reporting of elder abuse is affected by several factors, including how visible the signs of abuse are, the victims' expectation of outcome following disclosure (e.g. will they be believed or stigmatized), and being able to report the abuse (e.g. if there are physical and other restrictions preventing access to the police) (Fealy et al., 2012).

Abuse against older people occurs most frequently within the person's home (67%), followed by nursing homes (12%), residential care facilities (10%), hospitals (5%), and sheltered accommodation (4%) (Ogg and Bennett, 1992). The presence of abuse within care homes was confirmed in a study based on self-reports by nurses, 88% of whom had witnessed elder abuse in the workplace at least once and 12% on a frequent basis (House of Commons, 2004). Cooper and colleagues (2008) reported that 16% of members of staff in residential care facilities admitted to having engaged in some form of psychological abuse.

All these figures are likely to be underestimates given the low reporting rates by the victims. For instance, in a US study, Pillemer and Finkelhor (1988) found that only one in 14 cases of abuse was reported, while a UK study found that one among seven victims of physical abuse and half of the victims of verbal abuse disclosed their experiences (Homer and Gilleard, 1990). In a Canadian study, just one in 20 older people who had been financially abused reported it (Podnieks, 1993). While, therefore, prevalence rates vary, partly due to methodological challenges and

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differences, it is clear that elder abuse constitutes a significant problem worldwide.

Risk factors for elder abuse

A number of victim characteristics have been associated with elder abuse. These can be divided into six broad categories: i) mental health; ii) physical health; iii) ethnicity; iv) gender; v) age; and vi) living arrangements.

Mental health

Both psychological distress and the presence of a mental disorder increase the risk of victimization (Dong et al., 2008; Dong and Simon, 2008). For example, clinical symptoms of depression have been found to increase the risk of becoming the victim of abuse (Lachs et al., 1997).

Those with dementia are at particular risk of abuse with prevalence rates ranging from 28% to 52%. Severity of symptoms of psychosis, aggression, depression and anxiety (Cooper and Livingston, 2014; Conner et al., 2011), and higher care and dependency needs appear to be correlated to higher risk of victimization (Pillemer et al., 2016; Lachs and Pillemer, 2015; Dong, 2015; Murphy et al., 2013). There are some distinctive characteristics of abuse of people with dementia. More than one-third of victims were found to be the victims of multiple forms of abuse simultaneously (Wigglesworth et al., 2010). In addition to being victims, older people with dementia may also be perpetrators of abuse, either against their carers (Cooney et al., 2006) or against peers in residential care settings (Shinoda-Tagawa et al., 2004).

Following abuse, victims with dementia present with more frequent behavioural symptoms of distress, compared to older people without dementia (Burgess, 2006). In addition, mortality is higher (Dong et al., 2009) and may be partly accounted for by the overprescribing of antipsychotic drugs to contain behavioural symptoms (House of Commons, 2004).

The identification of abuse can be extremely challenging. Many behavioural symptoms and physical signs (e.g. social withdrawal, communication difficulties) can be misinterpreted as caused by the underlying disorder (Dong et al., 2014). Interview screening protocols may not be easily administered to people with deteriorating cognition, and, in fact, most existing screening tools have not been validated with this population (Wigglesworth et al., 2010). Even when identified, the perpetrators of abuse against older people with dementia are less likely to be prosecuted than those of victims who do not have dementia (Burgess, 2006).

Given the challenges of dealing with abuse against older people with dementia, efforts have focused on prevention strategies. The STRAteies for RelaTives (START), for example, is a psychological intervention to help

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with the stress and emotional burden experienced by family carers, and has proven effective in reducing abusive behaviours (Cooper et al., 2016; Livingston et al., 2013).

Physical health

Declining physical health is also associated with elder abuse (Biggs et al., 2009). Kamavarapu and colleagues (2017) reported that 49%–70% of older individuals who were the victims of abuse had physical impairments such as mobility issues, sensory impairment (loss of sight), and incontinence. Physical ill health was associated with increased financial abuse in the US, UK, and Canada (Laumann et al., 2008; O’Keeffe et al., 2007; Podnieks, 1993), with physical, sexual, and emotional abuse in Israel (Lowenstein et al., Enosh, 2009), and with neglect in the US, Canada, and Israel (Acierno et al., 2010; Amstadter et al., 2011; Burnes et al., 2015; Lowenstein et al., 2009; Pillemer and Finkelhor, 1988; Podnieks, 1993).

Ethnicity

Studies investigating ethnicity and elder abuse suggest that prevalence differences between groups relate more to help-seeking attitudes (i.e. how acceptable it is within the culture to seek help following abuse), rather than ethnicity per se. Proneness to help-seeking was found to be less common among Korean-Americans, compared to black people and white people, and this was explained in terms of the value attributed to behaviours that preserve family unity ahead of personal independence, typical of Korean culture (Moon and Williams, 1993).

Gender

As with women of all age groups, older women are exposed to a high risk of abuse. Although some researchers, including from Australia, Canada, Norway, Sweden, and the US, have carried out pioneering work in the field, gender-related issues in elder abuse have been often neglected (Penhale, 2003). In relation to older women with refugee status living in conflict zones, research and practice is even less advanced (United Nations, 2013).

The largest prevalence study around abuse of older women is the European Union prevalence study of Abuse and Violence against Older Women (AVOW) (Luoma et al., 2011), which found that 28.1% of women had suffered from any type of abuse, 23.6% from emotional abuse, 8.8% from financial abuse, 5.4% from neglect, 3.1% from sexual abuse, and 2.5% from physical abuse. Results from a study in China on older community dwellers found higher rates for physical abuse (6.3%), emotional abuse (28.4%) and neglect (13.8%), but a lower prevalence for financial abuse (1.9%) (Wu et al., 2012). A high prevalence of emotional abuse (33.7%) was confirmed in a Hong Kong study on intimate partner abuse (Yan and Chan, 2012). Women were also found to be more exposed than men to any type of elder abuse in studies carried out in the US

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(Laumann et al., 2008), the UK (Wood et al., 2010), Portugal (Gil et al., 2015), India (Chokkanathan and Lee, 2006), Ireland (Naughton et al., 2010), Israel (Lowenstein et al., 2009), and Mexico (Giraldo-Rodríguez and Rosas-Carrasco, 2013).

Being lonely and retired were the most relevant predictors of the victimization of older women (United Nations, 2013), and the most frequent perpetrators were their spouses and partners (Luoma et al., 2011). The most commonly reported consequences of abuse were found to be low quality of life, increased anxiety symptoms, and feelings of hopelessness, anger, and low self-esteem (Luoma et al., 2011).

Significant challenges in identifying abuse against older women are related to poor reporting rates. Barriers to disclosing abuse have been divided into internal (i.e. inherent to the individual) and external (i.e. inherent to the environment). Internal factors which can override the victim's need for safety and disclosure include self-blame, the need to protect the family unit and the children, feelings of powerlessness, and the fear of not being believed (United Nations, 2013). External variables comprise threatening attitudes and behaviour from the perpetrator, rejection from the family, and a lack of trust that law enforcement agencies can end the abuse (United Nations, 2013).

It has long been acknowledged that the impact of internal and external barriers, and indeed the abuse of older women as a phenomenon, can be better understood within a feminist framework. This perspective asserts that abuse is mediated by the inequity and power imbalance that sees women in a disadvantaged position compared to men in all societies and cultures (Nerenberg, 2006). Therefore, any prevention and intervention campaign, as well as legislative change, should promote equal rights in society for older women (Nerenberg, 2006).

Age

A lack of consistency is found in relation to victims' age. Several international studies reported a higher risk of abuse for the older age category (85 years old and above) compared to the younger group (65–85 years old) (Biggs et al., 2009; Giraldo-Rodríguez and Rosas-Carrasco, 2013; Gil et al., 2015; Naughton et al., 2010). However, research in the US found an association between younger age and increased risk for physical, emotional, and financial abuse and neglect (Acierno et al., 2010; Burnes et al., 2015; Laumann et al., 2008). Once again, these apparently conflicting findings are likely to be influenced by reporting and ascertainment issues in the various studies.

Living arrangements

Findings from the literature around living arrangements as a risk factor are also discordant. Some studies indicate that being married is a precursor for abuse in general (Pillemer and Finkelhor, 1988), and for emotional and physical abuse in particular (Podnieks, 1993; Soares et al.,

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2010). This can be explained by the shared living environment with the potential perpetrator (Wood et al., 2010). In line with this, Lachs and Pillemer (2015) reported that a higher number of household members increased the risk for elder abuse, in particular in the presence of poor income or financial difficulties, and when the family members were depending on the older person for housing and finance (Wood et al., 2010).

Other studies, however, found a correlation between not being married and being the victim of abuse, both for aggregated abuse (Giraldo-Rodríguez and Rosas-Carrasco, 2013; Naughton et al., 2010; O’Keeffe et al., 2007) and for any single type of abuse (Burnes et al., 2015; Laumann et al., 2008; O’Keeffe et al., 2007; Podnieks, 1993; Wu et al., 2012). Higher risk for victimization was also reported among older people who are lonely (Dong et al., 2007) and who lack social support (Amstadter et al., 2010).

Even less is known in relation to institutional settings (Lachs and Pillemer, 2015). In these settings, abuse may be perpetrated by a range of people, including members of staff and visitors (e.g. family, friends). Increasing interest has also been given to the phenomenon of elder abuse perpetrated by fellow residents, which seems to be more prevalent than abuse from staff (Pillemer et al., 2011).

Although for various reasons, including fear of retribution, abuse in institutional settings may pass unreported and unidentified (Kleinschmidt, 1997), the evidence suggests that abuse may be more prevalent than in the community (Pillemer et al., 2016) and increased by: i) organizational issues, including understaffing, inadequate training, and stress; ii) problems in staff-resident relationships, such as poor communication; iii) environmental factors, including poor health and safety; and iv) policy and regulations, such as an overly strict regime (Bennett et al., 1997). Therefore, adequate strategies (regulation, policies, management of the workforce) are crucial to ensure good practice in the workplace.

Several specific tools have been developed to investigate abuse in institutional settings. The Elders’ Psychological Abuse Scale (EPAS) (Wang et al., 2007) detects psychological abuse in long-term facilities, the Caregiver Psychological Elder Abuse Behavior Scale (CPEAB) (Hsieh et al., 2009) investigates violent behaviour as reported by staff of nursing homes, while the 24-item list of maltreatment/abuse acts (Cohen et al., 2010) is administered to the older residents. These context-specific tools may contribute to service improvement, as they represent an invaluable support for providers to identify when abuse is occurring.

Perpetrators of elder abuse

The explanatory model for elder abuse contends that risk is mainly affected by the perpetrator’s rather than the victim’s characteristics

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(Anetzberger, 2000). Ramsey-Klawnsnick (2000) divided perpetrators of elder abuse into five typologies:

1. The 'Overwhelmed', who may experience such high levels of emotional burden and stress in providing care to the older person (the caregiver stress hypothesis) that it can result in abusive behaviour.
2. The 'Impaired', who present with health issues that make them more prone to abusive behaviour. These include individuals with a history of mental or physical health problems, substance dependence, a history of serious psychiatric conditions such as personality disorder, or a history of offending (Laumann et al., 2008; Amstadter et al., 2011; Chokkanathan and Lee, 2006; Oh et al., 2006; Soares et al., 2010; O'Keeffe et al., 2007).
3. The 'Narcissistic', who are driven by personal gains to be derived from the abuse. The classic example is individuals who are unemployed and/or in financial difficulties and who depend financially on the victim (Wood et al., 2010).
4. The 'Bullying', who justify their abusive behaviour in terms of the victim not fulfilling their expectations. For example, health care staff may become perpetrators of violent behaviour against older residents who repeatedly fail to abide by the rules and regime of the residential home.
5. The 'Sadistic', who are prone to criminal behaviour and may have a history of serious offending (Lachs and Pillemer, 2015).

Overall, the perpetrators are more likely to be family members of the victims than not (Lachs and Pillemer, 2015). In institutional settings, however, Benbow and Haddad (1993) found that a large proportion of the perpetrators of sexual abuse were fellow residents. Differences in terms of gender are minimal. Ryan (2009) reported that 56% of perpetrators of abuse are male and 44% females. Wood and colleagues (2010) found no difference in the proportion of male and female financial abusers.

The impact of elder abuse

Although very limited research has looked into the consequences of elder abuse, its negative impact in several spheres of the victim's life is undisputed.

In relation to physical health, the consequences of abuse can be very serious for older people, given their frailty. A systematic review synthesizing data around the types of injuries following elder abuse reported injuries to the arms and shoulders (44%), face, teeth, and neck (23%), head (12%), legs and hips (11%), and torso (10%) (Murphy et al., 2013). There is also evidence of higher emergency department use (Dong et al., 2011) and hospitalization (Dong and Simon, 2013), and an increased mortality risk associated with elder abuse (Dong et al., 2013).

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Serious consequences are also reported for mental health with increased symptoms of depression, anxiety, and post-traumatic stress (Dong et al., 2013; Mouton et al., 2010; Gibbs and Mosqueda, 2010). These are often triggered by overall psychological distress, which is accompanied by feelings of shame, fear, guilt, denial, helplessness, and alienation (Booth et al., 1996; Goldstein, 1996). The severity of symptoms is associated with the type of abuse. Emotional and verbal abuse are more positively correlated with increased psychological distress, compared with physical abuse (Begle et al., 2011; Coker et al., 2002; Pico-Alfonso et al., 2006).

A negative impact on financial stability and quality of life can be the result of financial abuse among those who have limited income and for whom the loss of any amount of money leads to a failure to fulfil their basic needs (WHO/IPNEA, 2002; Alves and Wilson, 2008; Al-Baho, 2004).

Identifying elder victimization

Given their frequent contact with older people in a variety of settings, including general practices, emergency departments, hospitals, and surgeries, health care professionals play a central role in identifying elder abuse and violence (Wood et al., 2010). It is therefore crucial for these professionals to receive adequate training to raise their awareness of the issue, be educated on the identification of signs of violence, become aware of the resources available to intervene, and manage suspected cases effectively by liaising with the relevant agencies (Lachs and Pillemer, 2015; Shefet et al., 2007). Training should also be focused on encouraging sympathetic views and attitudes toward older people and on sensitizing staff to age-related issues (Pillemer et al., 2016).

The two main strategies for improved identification of elder abuse, which ideally should be combined for increased accuracy, are a clinical interview and a physical examination (Cohen et al., 2007). Before any of these assessments are undertaken, however, the health professional should assess the mental capacity of the older person. Where the person is deemed to be fully capable, the investigation can proceed, the older person becoming directly responsible for any choice made during and following the investigation (Wang et al., 2015). Where the person lacks capacity, a suitable person should be identified to help them—for instance, there may be a person, often a relative, with an enduring power of attorney. If it is suspected that the identified person is the perpetrator of the violence, the case should be referred to social services (Wang et al., 2015; see also Chapter 55 for further information about safeguarding).

The interview should ideally be undertaken with the older person separate from any potential perpetrator (Lachs and Pillemer, 2015) and should include an investigation of their personal context (e.g. culture, living arrangements, family characteristics) (Dong, 2015). The health professional undertaking the interview should adopt a sympathetic attitude and avoid being confrontational or drawing any conclusions

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before the facts have been ascertained (Lachs and Pillemer, 2015; Kleinschmidt, 1997).

A physical inspection of the older person can detect evidence of possible violence. There are typical signs that can indicate some form of violence, including scars, lacerations, bruising, burns, fractures, injuries, sexually transmitted diseases, decubitus ulcers, poor hygiene, dehydration, and malnutrition (Wyandt, 2004). Although none of these signs is unequivocally associated with violence, as they may be symptoms of a range of age-related conditions, they nonetheless provide visible evidence which may be relevant in future proceedings and should therefore be adequately recorded (Lachs and Pillemer, 2015). Where abuse occurs, physical signs are often accompanied by frequent medical appointments or visits to emergency departments and by some behavioural symptoms, which may include but are not limited to appearing fearful, withdrawn, nervous, and helpless (Wyandt, 2004).

In addition to clinical experience, health professionals can rely on several screening tools for violence. These include the self-report Vulnerability to Abuse Screening Scale (VASS) (Schofield et al., 2002), the ten-item tool for disclosure of abuse by Cohen and colleagues (2007), the Elder Abuse Suspicion Index (EASI) (Yaffe et al., 2008), the Elder Assessment Instrument (EAI) (Fulmer et al., 2004; Fulmer and Wetle, 1986; Fulmer et al., 1984) and the evident signs of abuse inventory (Cohen et al., 2006; Fulmer et al., 2004; Cohen et al., 2007; Cohen et al., 2010).

Reporting elder victimization

Several barriers may hinder the process of reporting violence towards older people. The older person may be reluctant to disclose violence or even to collaborate in an investigation, because they may feel guilty, embarrassed, ashamed, fearful of reprisal, afraid they may be relocated or institutionalized, or that they may not be believed (Burgess, 2006; Kleinschmidt, 1997). Language and cultural barriers may also play a part (Lachs and Pillemer, 2015). In addition, the criminal justice system might be unwilling to get involved due to uncertainties regarding the reliability of the older person as witness. It is therefore essential that support is available to the potential victim in this process.

Secondly, the consequences of violence, physical or emotional, can be easily misinterpreted as linked to normal age-related maladies, but false positives can also occur (Wyandt, 2004; Lachs and Pillemer, 2015). Some types of violence, namely sexual abuse, may pass undiagnosed, as they are not typically expected to occur in old age and might therefore be overlooked (Falk et al., 1997; Gray and Acierno, 2002).

Thirdly, health professionals might conceal abuse because of the sensitivity of the topic, an unawareness of the resources available to help, or simply to avoid detection of their own wrongdoing (Lachs and Pillemer, 2015). Even when reported, an investigation can take several weeks or

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even months, during which the health professional is required to make decisions in the face of ongoing uncertainties (Lachs and Pillemer, 2015).

Preventing elder victimization

As elder abuse and violence have become a global health concern, the World Health Assembly recently published a strategy aimed to reduce elder violence worldwide, through a collaborative action plan and joint initiatives (WHO, 2017). These include: i) increasing the evidence base and understanding of elder abuse, its types and its extent, particularly in low and middle-income countries; ii) developing guidance on how to respond to elder abuse; iii) sharing good practice across countries on how to prevent elder abuse; and iv) implementing collaborating networks worldwide to fight elder abuse.

Several strategies have the potential to prevent elder violence and abuse, although consistent evidence of their effectiveness is still limited (Ploeg et al., 2009; Sethi et al., 2011; Stolee et al., 2012). These strategies can be divided into interventions focused on single individuals (i.e. at-risk individuals or any potential perpetrator), and interventions focused on the community/society and in the workplace, especially care home settings.

Among the most common strategies in the first group are caregiver interventions, which aim to reduce carer burden, manage stress and increase social connection (Wood et al., 2010; Pillemer et al., 2016). Such interventions include peer and professionally-led support groups, psychological treatment (e.g. anger management), training on providing care (e.g. preparing meals), education on age-related issues, and respite care (finding temporary alternative care arrangements so that the primary caregivers can take time off their caring duties) (Wood et al., 2010; Pillemer et al., 2016).

Prevention strategies for potential victims can be non-specific (i.e. targeted to all types of violence or abuse) or specific (i.e. depending on the type of violence or abuse they aim to tackle). In the first group, telephone helplines represent a valuable resource to provide emotional and practical advice to potential victims. Phone helplines can also function as intervention (i.e. post-violence) strategies. They are staffed by volunteers or professionals and often work around the clock (Pillemer et al., 2016). In contrast with web-based chats, which require IT literacy, telephones are widely accessible, even in low-income countries. In relation to specific prevention strategies, money management training catering to older individuals who may be at risk of financial abuse provides older people with external support and assistance in carrying out financial routines, such as paying bills, manage shopping money, and banking (Pillemer et al., 2016).

Prevention strategies in the community and in society, such as mass media (television, radio, printed materials, and the web) campaigns, aim to promote a more positive image of older people as valuable members of

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the community, in order to stigmatize elder abuse. These initiatives include educating the younger generations (in schools, universities, and community settings) about the value of older people in society (Baker et al., 2016).

Prevention strategies in care homes include:

1. Identifying especially vulnerable individuals and implementing strategies to reduce their risk of victimization (e.g. offering low-stimulation environments to decrease challenging behaviours and aggression).
2. Increasing the knowledge and skills of members of staff to identify and deal with challenging behaviours (e.g. de-escalation training) to prevent violent responses against older individuals;
3. Creating a safe environment and culture of openness/support (e.g. through regular community meetings) to increase the confidence of staff and service users to discuss issues of violence and abuse;
4. Carrying out pre-employment background checks and closely monitoring members of staff, perhaps especially those at higher risk of becoming perpetrators (i.e. male, non-trained, front-line care staff) (Kamavarapu et al., 2017).

Intervening in cases of elder victimization

In order to tackle elder abuse, appropriate policies and laws are required, including local, national and international strategies to report and deal with violence affecting older people (Baker et al., 2016). The US has the most comprehensive advanced national system for the reporting and management of elder violence, which operates at the single-state level, and is supported by the National Centre on Elder Abuse at the federal level (Krug et al., 2002). Specific legislation to protect older victims is also in place in Canada, Japan, South Korea, Israel, and Slovenia.

In the UK, notification of suspected abuse to the relevant local authority, which is legally bound to make an enquiry, theoretically requires the consent of the victim. In most circumstances, however, this is bypassed (e.g. because of lack of mental capacity, ongoing risk to the victim, potential risk of the perpetrator to other members of the public, suspected violence within the NHS or professional care contexts) (Age UK, 2017), thus raising ethical dilemmas around the rights and autonomy of the individual. In Japan, Israel, and some states and provinces in the US, Canada, and Australia, the law mandates the reporting of elder abuse without the victim's consent (Wood et al., 2010).

Following the identification of violence, the primary goal of an intervention strategy is to ensure the victim's safety. This can be obtained through hospitalization (if the victim is in immediate need of health assistance), emergency shelters (when the victim needs immediate transfer to a temporary safe setting; Pillemer et al., 2016), and support groups. The secondary goal is to arrange support according to the

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person's needs, which usually is by means of multidisciplinary teams, given the multidimensional needs of older victims (Lachs and Pillemer, 2015). Multidisciplinary teams comprise a range of professionals with different fields of expertise, including the criminal justice system, primary physical, mental, and social health care, the legal system, financial services, and social and adult protective services. Such teams have been found to improve outcomes in addressing issues related to elder violence in a number of studies (Blowers et al., 2012; Navarro et al., 2013; Rizzo et al., 2015; Teaster et al., 2003; Ulrey and Brandl, 2012).

Conclusion

The existing knowledge gap around elder crime requires further research at various levels. Given the increasing diversity of the ageing population, this includes considering how cultural factors have an impact on elder violence. Community-based participatory research and research partnerships with stakeholders would enable researchers to better capture the cultural dimensions of the phenomenon (Dong, 2015). Collaboration between academic researchers and members of the public would also deepen the understanding of the impact that societal ageism has on the perpetration of violence and abuse against older people.

Another area requiring further research is that of effective interventions to prevent violence and abuse. A recent review of the evidence around prevention strategies found that only ten intervention studies had been carried out to assess the effectiveness of interventions for elder abuse, with all obtaining equivocal results (Pillemer et al., 2016). In addition, there is virtually no comparative international literature or cost-effectiveness analysis looking at the sustainability of existing interventions (Pillemer et al., 2016). In order to fill this gap and to determine which interventions (or elements of them) are really effective and financially sustainable, there is a need for high-quality randomized controlled trials carried out in both high-, middle-, and low-income countries (Baker et al., 2016).

Older people as perpetrators of crime

This section focuses on the existing evidence around older people as perpetrators of crime. The section opens with overall data around prevalence and types of crime, clinical characteristics of older offenders, and how elder crime is dealt with within different legal systems. It differentiates between older prisoners and older patients in forensic psychiatric settings. It presents and compares epidemiological data about each population against those of younger offenders. Finally, it discusses relevant issues around ageing in forensic settings.

Operational definition: Who is an ageing offender?

Before delving into what is known about ageing offenders and about their experience of the justice system, an operational definition of 'ageing offender' is necessary.

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Despite an ongoing debate around an appropriate age cut-off, given the highly subjective experience of the ageing process, old age forensic psychiatric and social health care researchers and practitioners generally set age 50 as criterion for inclusion in the older offender age group. This is based on evidence that ageing offenders experience poorer health and a quicker ageing process compared to people living in the community, for whom the United Nations set 60 years as criterion for older age (Natarajan and Mulvana, 2017; Cooney and Braggins, 2010). This is therefore also the cut-off we use in this chapter.

Prevalence of crime and type of offending in older people

It is generally accepted that offending peaks in younger age, adolescence, and early adulthood, though the gap between convictions in younger and older people might decrease over time. While most authors (e.g. Yorston, 2013; Natarajan and Mulvana, 2017) report that crime rates in older people appear to be stable over time with people over the age of 60 contributing approximately 1% to overall crime statistics, several countries have reported an increase in both newly convicted older people and older prisoners. For example, the number of prisoners over 60 years old in the Netherlands increased from 60 to 234 in the period 1994–2006 (van Alphen and Oei, 2010).

In England and Wales in 2003, sexual offences, theft and handling stolen goods, and violence (including homicide) were the three largest categories of indictable offences in those aged 60 and over, while among prisoners over 60 years of age nearly 60% were serving their sentence for a sexual offence (Fazel, 2014).

Rates of homicide committed by older people vary and should be interpreted with caution, given that they might be under-reported in certain settings (e.g. assaults between residents in care homes that result in death) (Yorston, 2013). In the UK, where homicide rates are among the lowest worldwide, the Office for National Statistics (ONS) (2018a) reported that in 2006, people over 55 years old were responsible for 26 homicides, accounting for 4% of the total number of homicides in the UK; in 2016, they were responsible for 11 homicides, accounting for 5% of the total. In contrast, in 2016, adults aged 45–54 were responsible for 23 homicides (10% of total); the percentage was even higher in the group 35–44 (50 homicides; 22% of total) (ONS, 2018a).

Compared to younger perpetrators, older individuals more frequently commit homicide against family members, particularly female spouses (Fazel et al., 2007). They are more likely to kill their victims through strangulation/suffocation (Hunt et al., 2010), and they have a higher prevalence of active psychiatric conditions affecting judgment and impulse control, including dementia and affective psychosis (Fazel and Grann, 2002). However, older perpetrators are less likely to be acting under the influence of substances (Hunt et al., 2010). The phenomenon of 'dyadic death' (i.e. suicide occurring after the homicide of the spouse) is

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more common among older than younger offenders (Fazel et al., 2007; Cohen et al., 1998). Motivations often include a fear of not being able to care for the other person any more in the face of illness and frailty, or the view that a disabled spouse may be better off dead.

Within forensic psychiatric settings, homicide is the commonest offence leading to admission (Yorston and Taylor, 2009; Shah, 2006; Lightbody et al., 2010; Coid et al., 2002). In fact, older patients in secure settings (60 years old and above) have an index offence of murder significantly more frequently than younger patients (16–59 years old), the ratio between the two groups being 5.71 (Coid et al., 2002). This might be explained by the fact that those with such offences stay longer and therefore they will eventually be part of the older group.

The ONS reported that in 2017, in 14% of the cases of rape or assault by penetration (including attempts), the offender was 40 years old and above; in 1% of the cases, the offender was 60 years old and over (ONS, 2018b). This figure is aligned with those of other countries. Despite the prosecution and convictions of older sex offenders having increased over time, such crimes might be underreported, because sexuality in old age is still a sensitive topic among many professionals working in hospitals and care homes (Yorston, 2013). Nonetheless, some studies in old age forensic psychiatry reported that sexual offences surpassed homicide as the primary offence leading to admission (Curtice et al., 2003).

The perpetrators of sexual offences are more likely to be male and the victims female (Curtice et al., 2003; Tomar et al., 2005). Compared to younger sex offenders, child sexual abuse was found to be much more prevalent in the older group (Yorston, 2013), but recidivism rates were lower (Fazel et al., 2006b; Barbaree et al., 2003). The sexual offence most likely occurs at home (72%) and in the presence of a psychiatric condition (33%) (Curtice et al., 2003). Hypersexuality and sexual disinhibition, which have a 17% prevalence in neurodegenerative condition such as dementia (Series and Degano, 2005), are also linked to an increased risk for sexual offences.

Acquisitive offences have been reported as among the commonest in older individuals and the most frequent reason for arrest in older people (Yorston, 2013). In a large study on ageing offenders, Needham-Bennett and colleagues (1996) found that theft accounted for 63% of all offences among people aged 60 years old and above, compared to 22% for all types of assaults, 10% for firearm, drug, and public order offences, and 4% for criminal damage. Shoplifting is the most prevalent among the acquisitive offences (58%) (Needham-Bennett et al., 1996). Offenders are as likely to be men as women, most likely to be single, poor, and unemployed, though perhaps surprisingly, people with higher levels of education are also over-represented (Lamontagne et al., 2000).

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Despite the high prevalence, most cases of acquisitive offences are not considered serious enough to be prosecuted and most older offenders (58%) are only cautioned (Needham-Bennett et al., 1996). As a result, less than one in three offenders (28%) were referred to welfare agencies (e.g. for psychiatric evaluation) in one study (Needham-Bennett et al., 1996). Given that engaging in shoplifting has been found to be associated with depression and fulfilment of psychological needs (Lamontagne et al., 2000), failure to offer offenders mental health treatment may result in an exacerbation of their symptoms (Yorston, 2013).

Clinical characteristics of older offenders

Older offenders can be divided into three distinct types (Natarajan and Mulvana, 2017): Those who start offending early and continue into old age, those who committed an offence earlier in their life and remain incarcerated into older age as a result, and those who commit their first offence at an older age. Only limited data is available about the number of offenders in each of these groups, though one US study (Steffensmeier and Motivans, 2000) suggested that, in prison, the second group was the smallest, with each of the other two groups accounting for over two-fifths of prisoners over 55 years.

We report on the prevalence of disorders in prison and secure forensic settings later in this chapter. Here, we briefly outline psychopathological characteristics of particular relevance to older offenders. Psychotic and mood disorders most frequently lead to the involvement of psychiatric services and, depending on the seriousness of the illness, to a transfer from prison to a hospital setting in all age groups.

Cognitive decline is a particularly important issue for older offenders, whether or not it occurs in the context of a formally diagnosed dementia. In addition to impairments in memory, typical of dementia, other symptoms may make the individual more prone to behavioural difficulties, including offending, such as disinhibited behaviour, lack of judgment, and impairment in executive function (e.g. a lack of planning and impulse control). These symptoms may result in reactive (as opposed to planned) aggression (Yorston, 2013). On the other hand, personality disorder symptoms, which may also include impulsivity, are generally regarded to decrease in severity with age, though changes in life circumstances as may occur in older people might lead to an exacerbation of symptoms. While of importance in all ages, an interview with an older person's relative or carer to identify any changes in behaviour is especially crucial.

When assessing and managing risk in the context of these disorders, practitioners need to consider the potential limitations of risk assessment tools, which have been standardized with younger populations. This is particularly so with actuarial risk assessment tools, which predict risk according to percentages of those who go on to reoffend or allocate offenders to high, medium or low risk bands. The presence of cognitive impairment/dementia could both increase (e.g. through an increase in

Older people as victims and perpetrators of crime

impulsivity) and decrease (e.g. through apathy, lack of opportunity) risk (Natarajan and Mulvana, 2017). A detailed, individualized assessment using a structured professional judgment approach, including a formulation of the risks (type and severity of risk, triggers, motivators, inhibitors, protective factors) and their management, is required in each case.

The route to prison and forensic psychiatric services

Although different countries adopt different legal systems and procedures, the general principles around the detention and care of offenders are similar (Edworthy et al., 2016; Salize et al., 2005). Once an individual is charged with an offence, three options are available: acquittal, punishment, or diversion into a treatment setting, including hospital admission (Völlm et al., 2017a). A prerequisite for punishment is criminal responsibility for the offence, the criteria for which may vary across jurisdictions (Völlm et al., 2017a). If criminal responsibility is present, the offender can be sentenced, including to imprisonment.

If not deemed fully responsible for the criminal act, the offender is either acquitted or required to undergo some type of forensic psychiatric treatment (Völlm et al., 2017a). In order for the offender to have access to treatment, in most European countries a degree of reduced responsibility is a prerequisite (Völlm et al., 2017a). There are some exceptions, however, for example, in the UK, where admission to forensic psychiatric care can occur regardless of criminal responsibility and can be ordered based solely on the person's mental condition at the time of assessment (Konrad and Völlm, 2010). In addition, some countries allow transfer from prison to forensic psychiatric settings, if the detainee develops a psychiatric illness which requires specialist care. The mentally disordered offender (MDO) may then later move back to prison, though more frequently, they remain in the treatment setting.

Psychiatric treatment for MDOs can be offered as in-patient services, out-patient (i.e. community) services, or within the prison system. In most jurisdictions, excluding countries such as Italy, Croatia, and Portugal, offenders in in-patient forensic psychiatric units can be detained beyond the length of the prison sentence they would have been given for the same crime, had they not been mentally disordered (Völlm et al., 2016).

However, the majority of mentally disordered offenders are found within the prison system, even in jurisdictions where specialist services exist (Völlm et al., 2017a). Provision equivalent to care in the community is the guiding principle of prison care, as per the United Nations Standard Minimum Rules for the Treatment of Prisoners and the UN Convention on the Rights of Persons with Disabilities. It is questionable, however, to what extent different countries operate in full compliance with the standards prescribed (Gee and Bertrand-Godfrey, 2014).

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In-patient forensic psychiatric services are offered in most countries at different levels of security, based on the risk that the patient poses to themselves or others (Salize et al., 2005), but there are notable exceptions. In Italy, in-patient forensic psychiatric services are offered in residential units at one single (low) level of security (Di Lorito et al., 2017a,c). In addition to a degree of security, other common elements of in-patient forensic psychiatric services are medical, psychological, and social interventions offered by multidisciplinary teams (Tapp et al., 2016).

Out-patient services offered in the community are available in a limited number of countries, including Austria, Belgium, Germany, the Netherlands, the UK, and Poland (Heitzman and Markiewicz, 2017; Sugarman and Oakley, 2012; Salize et al., 2005). These provide treatment to offenders equivalent to that offered to non-offending community citizens, one important difference being that it can have elements which are mandated by the courts (Völlm et al., 2017a).

Issues relating to arrest, interviewing, and trial in older offenders

Several authors have suggested that older offenders were previously dealt with differently by the criminal justice system, in particular that they were less likely to be arrested and charged due to issues around fitness to plead and an assumption that older people pose less of a risk to society compared to younger offenders (Yorston, 2013). However, given the increase in older offenders (as outlined in this chapter), this seems to have changed in recent years. Older people who appear to have a mental health problem affecting their ability to participate in proceedings, like vulnerable younger offenders, should have the right to be accompanied by an 'appropriate adult' when interviewed by the police, to ensure that they understand what is happening to them and why (e.g. Police and Criminal Evidence Act, 1984 for England and Wales).

When standing trial, the first, requirement before criminal responsibility can be considered, is to determine whether the defendant is fit to plead and stand trial (i.e. 'fitness to plead' in the context of UK law or 'competence to stand trial' in US law). This is to ensure that the defendant has a fair trial (i.e. he/she is able to participate effectively in the proceedings). In UK law, as an example, criteria for fitness to plead are (Rogers et al., 2008):

- ability to plead
- ability to understand the evidence
- ability to understand the court proceedings
- ability to instruct a lawyer
- knowing that a juror can be challenged.

Fitness to plead can be affected by both mental and physical abilities. Examples of the former include cognitive functioning or delusional thinking, while sensory impairment can also affect someone's capacity to

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follow proceedings. It is important that arrangements are made to achieve fitness to plead where possible, for example, through adjustments of the proceedings (e.g. shorter sessions) or visual/hearing aids. When fitness to plead is in question, the defendant is likely to be assessed by a psychiatrist, who will be able to comment on possible adjustments. The assessment is the same for older and younger individuals, but issues like cognitive functioning, including memory and executive function, as well as physical impairments, are likely to play a more important role in older defendants.

Ageing Prisoners

Prevalence

Since 2000, the general prison population worldwide has grown by about 6% (Walmsley, 2016). In some countries, such as Spain, offenders are released from prison at age 80 and in Azerbaijan and Russia life sentences cannot be given to people over 65 years old (Penal Reform International, 2015). However, in most countries worldwide the number of ageing prisoners has markedly increased, representing the fastest growing group (Joyce and Maschi, 2015; Davoren et al., 2015; Cornish et al., 2016).

In the period 2000–2010, for instance, the number of ageing inmates in Australia increased by 36% (Baidawi, 2015) and in Canada by 50% (Penal Reform International, 2015). In the period 2002–2011, Japan experienced an increase of around 100%, while in the US, the number of ageing prisoners increased by a record 300% (Williams et al., 2012). In the UK, a 169% increase in the population of prisoners over 50 years old was reported in the period 2002–2016, while the percentage of prisoners below 20 years old decreased from 13% to 6% between 2005 and 2016 (Allen and Watson, 2017).

Ageing prisoners now constitute 10% of the total prison population in Ireland (Joyce and Maschi, 2015), 15% in the UK (Allen and Watson, 2017), 19% in the US (Carson, 2015), and 25% in Italy (ISTAT, 2015). At the end of 2016, the UK prison system even had one prisoner aged over 100 years (Allen and Watson, 2017).

The phenomenon of an increasingly older prison population is caused by several factors (Frazer, 2003). Longer life expectancy and fewer releases by parole boards have reduced the turnover and led to an accumulation of ageing detainees (Senior et al., 2013). Societal attitudes toward ageing offenders have become less lenient. Crimes that were seldom reported to the authorities in the past, such as sexual offences, are now more frequently prosecuted (Frazer, 2003, Yorston, 2015b). Advances in forensic evidence caused a 95% increase between 1995 and 2005 in the charge and incarceration in old age of people who have committed historical offences (RECOOP, 2017). At the same time, in some countries, tougher sentencing policies have been adopted to discourage crime, and

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ageing offenders are receiving life sentences more often than in the past (Frazer, 2003; Moll, 2013).

Psychiatric morbidity

While prisoners of all age groups experience poor mental health (Baldwin and Leete, 2012; Cooney and Braggins, 2010; Moll, 2013), the added challenges of ageing in restrictive settings and the poor physical, mental, and social health care provision may further expose ageing prisoners to deteriorating mental health. Although limited epidemiological research exists, a recent systematic review and meta-analysis synthesizing the existing international evidence found that almost 40% of ageing prisoners experience at least one psychiatric disorder, including depression (28.3%), alcohol abuse (15.9%), and psychoses (5.5%) (Di Lorito et al., 2018b). The prevalence reported in the overall prison population (i.e. all ages), based on 109 studies including 33,588 prisoners in 24 countries, was 11.4% for depression and 3.7% for psychosis (Fazel and Seewald, 2012). In relation to alcohol abuse, an international systematic review based on 13 studies on the overall prison population reported an 18–30% prevalence for male prisoners and a 10–24% prevalence for female prisoners (Fazel et al., 2006a). We can therefore conclude that, compared to prisoners of all ages, in the older prisoners' group depression and psychoses are more prevalent and alcohol abuse is less prevalent.

When comparing data from the older prison population against the prevalence found among ageing people in the community, a greater Relative Risk (RR) was found for most psychiatric disorders, including depression, schizophrenia/psychoses, bipolar disorder, cognitive impairment, personality disorder, anxiety disorders and PTSD (Di Lorito et al., 2018c). The RR was highest for schizophrenia/psychoses, evidencing that ageing prisoners may potentially experience more severe psychiatric conditions (Di Lorito et al., 2018b).

Conversely, the RR was not statistically significantly higher for dementia (Di Lorito et al., 2018b). This may be due to several factors: i) lack of systematic cognitive assessment within the prison system (Moll, 2013); ii) a prison culture oriented towards principles of punishment rather than care, which, in the absence of geriatric training among prison staff, may hinder the identification and diagnosis of the condition (Moll, 2013); and iii) lower incarceration rates or diversion from prison for offenders with dementia (Natarajan and Mulvana, 2017).

Suicide rates are also markedly high among ageing prisoners. Handtke and Wangmo (2014) found that 50% of ageing prisoners engage in suicidal thinking, as they may come to such a level of despair and alienation from life that they view death as the only possible escape from their misery. Although younger age has been identified as a risk factor for self-harm in the general population (Hawton et al., 2014), a large UK

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study reported that 'only' 30% of male prisoners aged 16–20 years old had engaged in suicidal thoughts in the previous year (Lader et al., 2000).

The challenges of ageing in prison

A recent systematic review of 25 international studies around the individual experience of ageing prisoners (Di Lorito et al., 2018c) reported that despite emerging examples of good practice, the inadequacy of the prison system to respond to the unique physical and social health care needs of ageing prisoners has a detrimental impact on their overall experience of imprisonment (Aday, 1994; Lemieux et al., 2002; Smyer et al., 1997). In the UK context, these findings confirmed previous evidence gathered by the prison inspectorate (HM Inspectorate of Prisons, 2013). This report commented that, although prison services are becoming a key accommodation and care provider for ageing offenders, little emphasis is placed on the rehabilitation and needs of this population (HM Inspectorate of Prisons, 2013).

Currently, most prison institutions across the world are affected by common barriers that hinder care provision. Among these is what has been defined by Crawley (2005) 'institutional thoughtlessness', the widespread neglect of mental and social care health needs of ageing prisoners. Institutional thoughtlessness is partly explained in terms of untrained prison staff. Although some initiatives, such as the Community Ageing Health Project in the US, have delivered geriatric training to all professionals working in the justice system (Ahalt and Williams, 2015), most prison staff are unable to appreciate the difficulties that the prison regime presents to ageing prisoners or, if they do acknowledge the problems, they may feel powerless to act.

The neglect of ageing prisoners' needs is further caused by a macho prison culture, which views care duties as feminine and makes staff reluctant to undertake them (Moll, 2013). In addition, compared to the younger inmates, who are often more assertive self-advocates, ageing prisoners appear more reserved and often reluctant to disclose their needs, which may therefore pass unnoticed (Doron, 2007).

Further challenges are presented by declining physical health. Ageing prisoners have been evidenced to present with greater mobility needs compared to both younger prisoners and ageing individuals in the community, and more than 80% suffer from chronic conditions or disability (Natarajan and Mulvana, 2017). Prison institutions do not seem able to respond adequately to the ageing prisoners' accessibility needs, often providing inaccessible prison cells and bathrooms, narrow doors, and key facilities (i.e. healthcare offices) located on the upper floors of century-old buildings (Senior et al., 2013; Crawley, 2005; Joyce and Maschi, 2015). This is in contravention of the UK Disability Discrimination Act 2005.

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Some examples of good practice, however, are emerging. For example, Her Majesty's Prison (HMP) in Norwich in the UK offers an in-patient healthcare facility for ageing prisoners, and HMPs Frankland, Kingston, and Whymott have dedicated wings for ageing prisoners (Natarajan and Mulvana, 2017). In the US, specialist services for ageing prisoners are common, including the creation of specialized units or wards for people living with dementia or the implementation of peer-support programmes to promote the inclusion and independence of prisoners in need (Moll, 2013). However, much remains to be done for current prison services to be considered dementia-friendly (Joyce and Maschi, 2015).

In relation to the activities offered in the prison system, Senior and colleagues (2013) reported that, in England and Wales, only half of the recreational programmes were suitable for ageing prisoners, while 67% were not accessible for anyone with mobility issues. Because of these barriers to taking part in activities, ageing prisoners may become reluctant to venture out of their cells and in turn develop feelings of social isolation and disengagement, which may have a negative impact on their process of rehabilitation (Crawley, 2005). The frequent loss of family contact experienced by ageing prisoners, and the death of partners or spouses, only add to the risk of alienation from life (Moll, 2013; Crawley, 2005).

The process of release into the community may also be more problematic for older prisoners. One study found that 50% of ageing ex-prisoners ended up homeless and destitute (Senior et al., 2013; Joyce and Maschi, 2015), compared to 30% for the overall (i.e. all ages) prisoner population (Niven and Stewart, 2005). The lack of systematic pre-release courses tailored to the unique needs of ageing prisoners and the poor liaison between prisons, probation services and offender managers often leave them unprepared to face the challenges of life in the community (Senior et al., 2013).

Ageing forensic psychiatric patients

Ageing forensic psychiatric patients represent a minority of the patients living in secure institutions. Nonetheless, as for ageing prisoners, given the recent changes in cultural attitudes toward ageing offenders (Yorston, 2015b; Frazer, 2003), the ageing trends in the population (Senior et al., 2013) and a tougher approach to crime (HM Inspectorate of Prisons, 2008), their number is on the rise.

In a UK study carried out over 20 years ago at Broadmoor Hospital (one of the three UK high-security services), 8% of patients were aged 60 years old and above (Wong et al., 1995). At the present time, in Rampton Hospital (another UK high-security service), one patient in five falls within this age category (Di Lorito, et al., 2019b). This trend, however, is not specific to the UK context, as similar prevalence rates have been reported elsewhere. In Italy, for example, in a single-site case study on ageing forensic psychiatric patients, Di Lorito and colleagues (2017b)

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reported that 20% of the patients were over the age of 50. In Germany, 20% of all patients in forensic-psychiatric hospitals and substance misuse units (in Germany different sections apply to those with offending related to substance misuse) are over 50 years old (Dönisch-Seidel, personal communication).

Despite this increasing prevalence, research around older forensic psychiatric patients remains scant.

Demographic data

Available data suggest that in terms of gender composition, the overwhelming majority of older patients in secure care—at least 85%—are males. In our study at Rampton Hospital, one of the three high security units in the UK, 89% of the patients were male, a male to female ratio of over 8:1 (Di Lorito et al., 2019b). This is not greatly different from younger patients: Coid and colleagues (2002) found that around 85% of patients aged below 60 years old in secure settings were male.

In relation to marital status, a significantly smaller percentage of patients over 60 years old were single (31%), compared to patients under 60 years old (73%) (Coid et al., 2002). In relation to ethnic composition, white patients were found to be most prevalent, making up to 100% of the sample in the UK studies (Curtice et al., 2003; Lightbody et al., 2010; Yorston and Taylor, 2009). The proportion of white ethnicity was higher among older patients (88%) than younger patients (75%) (Coid et al., 2002).

Contact with services

Older patients typically have long admissions, ranging from an average of 14 years (Lightbody et al., 2010) to 26 years (Shah, 2006). This is longer than for either prisoners sentenced for the same offence or for patients in general psychiatric services with a similar mental disorder (Völlm et al., 2016). A recent study on long-term patients in medium and high-security hospitals found a positive correlation between age and length of stay (Völlm et al., 2017b).

Coid and colleagues (2002) reported that 11% of 61 patients over 60 years old in medium and high secure forensic psychiatry services in the UK over a seven-year period were admitted following non-criminalized behavioural disorder, compared to 28% of younger patients. The same authors found a statistically significant lower percentage of older patients admitted to high security (3%), compared with the younger patients (15%) (Coid et al., 2002).

The majority of older patients (65%) had previous psychiatric admission (Paradis et al., 2000; Lightbody et al., 2010), whose number averaged two (range 0–10) (Yorston and Taylor, 2009). However, previous psychiatric admission of older offenders was significantly lower than younger offenders according to Coid and colleagues (2002), who also found that

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23% of older patients had been in prison, a lower percentage than among the younger offenders. Prison transfers amounted to up to 60% in a UK study on long-stay patients (Völlm et al., 2016).

Mental health

Yorston and Taylor (2009) found that 36% of patients over 60 years old in a UK high-secure service had schizophrenia, 27% delusional disorder, and 9% schizoaffective disorder. High prevalence of psychotic illness was also found in a retrospective study of older patients residing in secure psychiatric settings in Scotland between 1998 and 2007, with an aggregated prevalence of 64% for schizophrenia, schizotypal and delusional disorders (Lightbody et al., 2010). However, Coid and colleagues (2002) found that the prevalence of schizophrenia was significantly lower in older patients (33%), compared to younger patients (58%). Conversely, the older patients had a significantly higher prevalence of delusional disorder.

Personality disorder was found to be the most prevalent psychiatric disorder among older patients in a cross sectional study carried out in three secure settings in the UK (61%) (Di Lorito et al., 2019b). The older patients had significantly higher prevalence of schizoid personality disorder, as opposed to the younger patients, who were more frequently diagnosed with antisocial and borderline personality disorder (Coid et al., 2002). Lifetime prevalence of depression was 42% for older patients, compared to 18% for younger patients, the difference being statistically significant (Coid et al., 2002). The difference may indicate that the added challenges of ageing in secure settings may expose the older patients to being vulnerable to psychiatric disorder.

Paradis and colleagues (2000) found that 33% of the older patients were affected by some type of dementia (2% with Alzheimer's disease). Similar findings were reported by Shah (2006), who found a dementia prevalence of 27%. One study reported a prevalence of below 10% (Tomar et al., 2005). Organic brain syndrome was statistically significantly more prevalent in the older patients (33%) compared to the younger ones (12%) (Coid et al., 2002). However, only a small percentage (less than 20%) of older patients had undergone any formal cognitive testing (Curtice et al., 2003; Lightbody et al., 2010). Thus, the rates reported could underestimate the extent of the problem. Regardless, the higher rates of dementia in forensic secure settings compared to the prison system might indicate that diversion into psychiatric care might be more appropriate for this patient group.

A formal diagnosis of alcohol abuse appears to be relatively uncommon, around 3% to 6% of older patients (Curtice et al., 2003; Paradis et al., 2000). However, the rates were much higher if regular consumption was considered (41%) (Curtice et al., 2003). Coid and colleagues (2002) found no significant differences compared to the younger patients, and the prevalence of drug abuse and dependence among older patients was

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much lower than among younger patients (0% and 52%, respectively, though these figures are likely to have changed since the time of that study).

Physical health

Forensic psychiatric patients of all ages experience poorer physical health and have a shorter life expectancy (10–20 years less) compared to people living in the community (Davies, 2013). In addition, older patients may be affected by age-related conditions, which exacerbate their overall physical wellbeing.

Curtice and colleagues (2003) found that 44% of older patients had one health problem and 16% had two or more. On average, each patient had one to two diagnoses of physical illness upon admission, which increased to more than two upon discharge (Shah, 2006; Lightbody et al., 2010). Mobility problems were prevalent, affecting up to 61% of the ageing patients in one study (Lightbody et al., 2010). One-fifth of the sample suffered from sensory impairment, including hearing (16%) and eyesight problems (6%) (Curtice et al., 2003). Cardiac disease, hypertension, and diabetes were also widespread, with a prevalence of 23%, 15%, and 13%, respectively (Paradis et al., 2000).

Qualitative studies

Very limited data exist around the individual experience of ageing patients in forensic settings at the international level. One common theme emerging from studies carried out in the UK and Italy (Yorston and Taylor, 2009; Di Lorito et al., 2017b, 2018a) is the challenges of life in confinement and how the limitations to freedom have a negative impact on the experience of ageing patients. For example, patients complain about the rigidity of policies around gender separation, which do not reflect the reality of life in the community and are therefore believed to hinder successful reintegration into life outside the institution (Yorston and Taylor, 2009; Di Lorito et al., 2017 b, 2018a).

Given the challenges of life in secure settings, ageing patients adopt a variety of coping mechanisms, the most reported of which is relying on strong support networks (Yorston and Taylor, 2009; Di Lorito et al., 2018a). In this sense, the clinical team on the ward plays a central role in promoting the emotional wellbeing of the patients, given the extended time they spend with them on a daily basis (Dutta et al., 2016). In fact, several patients reported how, in times of difficulty, they preferred to talk to the staff on the ward (e.g. nurses), rather than wait for psychology consultation (Yorston and Taylor, 2009). Older patients generally appreciated the effort of the members of staff on the ward to go beyond traditional work duties and develop genuine relationships with them, which enhances both clinical rapport and the therapeutic journey of the patients (Di Lorito et al., 2018a, 2019a).

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Peers may also represent a source of support. Although most patients reported having a special friend or a small group of friends to confide in, they acknowledged that the common mental health symptoms may hinder good rapport at times (Di Lorito et al., 2017b). Similar mixed feelings apply to their relationships with younger patients. While several older patients appreciated the balance and diversity of mixed (i.e. younger and ageing) wards, others reported irreconcilable differences and called for the creation of separate wards for ageing patients (Di Lorito et al., 2017b). Another argument in support of the creation of aging patients' wards is related to the unique care needs of this population, treatment and security, and the barriers to addressing these in mixed ward environments. For example, some occupational therapists raised concerns about fitting handrails to aid ageing patients' mobility, as they thought these would present security issues for the younger patients (Yorston and Taylor, 2009).

In relation to personal resources to deal with the difficulties of life in confinement, older patients frequently reported a strong sense of spirituality, which provides them with inner peace and comfort (Di Lorito et al., 2017b). This was in contrast to younger patients, who may be reluctant to voice a religious dimension to their life. In order to find the emotional strength to deal with their present difficulties, older patients also resort to positive thinking, by recalling happy memories or imagining a future life outside the institution (Di Lorito et al., 2017b, 2018a).

Ageing patients also emphasized the importance of getting off the ward to boost their recovery. Although the existing programmes of vocational, educational, and cultural activities were generally found to be satisfactory, some patients wished to be more involved in the development and design of age-friendly activities (Di Lorito et al., 2017b, 2018a; Yorston and Taylor, 2009). Pressures on budgets and staffing levels, experienced by most forensic psychiatric systems worldwide, are therefore likely to be a significant barrier to improved services for older patients. Issues of security may also represent a challenge to implementing recovery-oriented activities in more restrictive settings.

Discharge from the service is also a challenge for the mental wellbeing of older patients, many of whom have spent a long time in the service. Several patients reported developing emotional attachment to the institution, and anxiety at the uncertainty of future prospects (Yorston and Taylor, 2009). This may be particularly so in legal systems, such as the UK, where some patients may be transferred back to prison after their discharge from the mental health service. These challenges may be difficult to overcome and require extra effort on the part of the multidisciplinary team to encourage the patients to move along their pathway (Yorston and Taylor, 2009). Therefore, older patients who have been in the service for a long time need careful attention and tailored individual discharge plans (Yorston and Taylor, 2009).

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Conclusion

The United Nations has identified ageing offenders as a special need population, owing to their unique physical, mental health and social care needs (Atabay, 2009). This requires the development of adequate strategies to ensure improvement of forensic service provision for this population.

One option that could address the unique needs of older offenders is the development or further implementation of services specifically catering for older offenders, both within the prison system and in the forensic psychiatric sector (Tomar et al., 2005; Nnatu et al., 2005). Some argue that separate services for older offenders are not ethically acceptable, as these may cause segregation and have unsustainable costs; they advocate in favour of mixed-age services, which may have added benefits (e.g. a calming effect of older individuals on younger ones, locality rather than distance of services from home area) (Di Lorito, et al., 2019a). Others instead emphasize the benefits of specialist care provided by adequately trained professionals and view dedicated services as safer environments, with reduced risk for bullying and victimization (Natarajan and Mulvana, 2017). Super-specialization of forensic services with minority populations, such as women, people with learning disabilities, and deaf people, has so far proved effective in boosting service users' experience, and represents a further argument in favour of dedicated services for older offenders (Natarajan and Mulvana, 2017). Furthermore, these services might offer end-of-life and palliative care to address the intensive care needs of offenders with progressive conditions, who cannot be released in the community on compassionate grounds, given their risk.

In the ongoing debate around specialist care provision, some implications for service improvement in the current mixed-age units can be derived. In order to boost opportunities for recovery of older offenders, services should further develop: i) specialist expertise through staff training; ii) age-relevant treatment and activities; and iii) age-friendly environments. Expertise in forensic mental health and in geriatric issues are a key requirement for staff dealing with older offenders (Natarajan and Mulvana, 2017). Sensitizing all members of the multidisciplinary team to age-related needs requires a change of culture, with a greater balance between duties of restrictiveness and care. The emphasis on rehabilitation through care is typical of strength-based frameworks such as the Good Lives Model (Chu and Ward, 2015; Robertson et al., 2011) and the Recovery model (Drennan et al., 2014), which are recommended across all forensic settings. Forensic services need to offer treatment and activities which better respond to the unique rehabilitation/recovery needs of older offenders, such as Cognitive Stimulation Therapy (CST), reminiscing, speech and language therapy, physiotherapy, and mobility work (Di Lorito, et al., 2019a; Natarajan and Mulvana, 2017). Finally, to promote independence in the presence of deteriorating physical and mental abilities, modifications to the environment and the daily routine may be necessary. These include orientation aids/cues to facilitate

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navigation within the premises, more frequent daily planning meetings, and special furniture (e.g. shower chairs, handrails) (Natarajan and Mulvana, 2017).

Service improvement should be supported/informed by dedicated policy on older offenders, which has only been developed in few countries thus far. In Ireland, for example, the Prison Service Strategic Plan 2016–2018 includes the development and implementation of the first national strategy on older prisoners (Joyce and Maschi, 2015). In other countries, standards of health care provision for ageing offenders are aligned to principles and guidelines established in international human rights documents, such as Article 3 of the European Convention of Human Rights (ECHR), or based on general national policies. In the UK, equality in the treatment and care of ageing offenders is granted through the National Institute for Health and Care Excellence (NICE) guidelines on mental wellbeing and independence in ageing people (NICE, 2015) and the Care Act 2015. The latter document, for example, establishes the responsibility for local authorities to provide equal social health care to all older individuals.

In the absence of dedicated strategies, however, these general policies do not seem sufficient to ensure consistent levels of quality in service provision across different institutions. At present, the existing examples of good practice are largely dependent on the commitment of individual institutions and the enthusiasm of staff (Yorston, 2015a). In order to ensure uniformity in quality standards and promote good practice, accumulating evidence suggests that policy makers should take initiative at the governmental level and develop specific national strategies to address the unique needs of older offenders.

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Driving and psychiatric illness in later life

Chapter: Driving and psychiatric illness in later life

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Overview of mobility and health

Mobility and driving evoke a curious response in health care personnel. With most areas of function, we assess and treat people so as to maximize that function. The literature on driving and disease, however, has until recently been biased in favour of the identification of those who should not drive, rather than maximizing health and function so that older people can participate and integrate maximally with society (O'Neill et al., 2011). This matter assumes great importance in view of the dramatic rise in the proportion of older people in our society. It is further emphasized by the enormous increase in the numbers of older people who wish to continue driving, given the changing age demographic and increased access to the motor vehicle. In the United States (US), at successive White House Conferences on Aging, transportation has been rated as enormously important in older people's lives, even prioritized over Medicare and Medicaid (Carp et al., 1980; White House Conference on Aging, 2005).

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This is backed up by the finding that problems with transportation form a major barrier to healthcare access (Okoro et al., 2005; Syed et al., 2013).

Some of the negative attitude to older drivers stems from a more widespread failure to appreciate the idiosyncratic and often paradoxical approach of our society to mobility and safety. Despite high-profile campaigns to promote safety on our roads by way of exhortations to reduce speed and avoid alcohol, at virtually every level of transport policy, mobility takes priority over safety. If safety were paramount, the speed limit would be 20 miles per hour and governors would be fitted to car engines prevent this speed limit from being breached. It is also likely that we would have a more graduated entry to driving while in the late teens or early twenties (Masten et al., 2011). This is because youth and inexperience breed risky driving behaviours that cause crashes. In contrast to the emphasis on mobility over safety for youth, there is an unfortunate emphasis of many governments on stigmatizing older drivers, emphasizing safety over mobility, in the absence of evidence (White and O'Neill, 2000; Mitchell, 2008). Older drivers are forced to undergo regular medical checks in most countries of the European Union, despite evidence that this practice is harmful (Hakamies-Blomqvist et al., 1996; Langford et al., 2004) or ineffective (Rock 1998). This ageist legislation is not based on any factual evidence and reflects the weakness of organized advocacy for older people. This is despite the fact that older drivers have one of the best safety records of any group of drivers in society (Evans, 1988).

Sometimes a U-shaped curve is displayed showing that older drivers have a higher crash risk per mile than younger drivers do (Broughton, 1988). This is spurious for several reasons. Not only do older drivers drive considerably fewer miles than their younger peers, but several studies have shown that this finding is an artefact of low mileage, possibly as a result of higher proportion of trips on non-freeway (or non-divided-lane) roads—if low mileage is controlled for in comparisons with younger drivers, the difference in crash rate disappears (Hakamies-Blomqvist et al., 2002; Langford et al., 2006, 2013). In addition, the crash risk in all other actuarial settings is per year, rather than on distance travelled. Finally, old people are more fragile and are more likely to suffer death or serious injury for a given severity of crash than young people are (Brorsson, 1989; Lyman et al., 2002).

Health and driving

There is a famous illustration in Goodman and Gilman's pharmacology textbook that illustrates the process of absorbing a new medication into medical practice. This oscillates from an initial enthusiastic acceptance to a sceptical rejection, and then finally there is a reasoned assessment of the positive and negative aspects of the drug (Fig. 57.1). This is a similar process to that which occurs when healthcare professionals encounter the concept of driving and illness for the first time. At the outset, working in an environment where a highly selected population are much more

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likely to have a high burden of disease, it is inevitable that the potential risks should be perceived first rather than the impact on mobility of driving cessation (O'Neill et al., 1992). As the researchers in the area gain perspective, a totally different concept comes to the fore—that of the major threat posed to the mobility of older people by age-related disease (Metz, 2000). Finally, the fusion of both points of view is achieved, whereby an enabling process is developed which encompasses the mechanisms for helping those who can no longer drive to seek alternative methods of transport, secure in the knowledge that they had due process in a thorough evaluation and remediation (O'Neill, 2000). In a welcome development for the new millennium, this more balanced approach has been adopted by the Organization for Economic Cooperation and Development (OECD, 2001), the European Conference of Ministers of Transport (CEMT, 2001), the US Transportation Research Board (2004), and Transport Canada (Road Safety Canada Consulting, 2011).

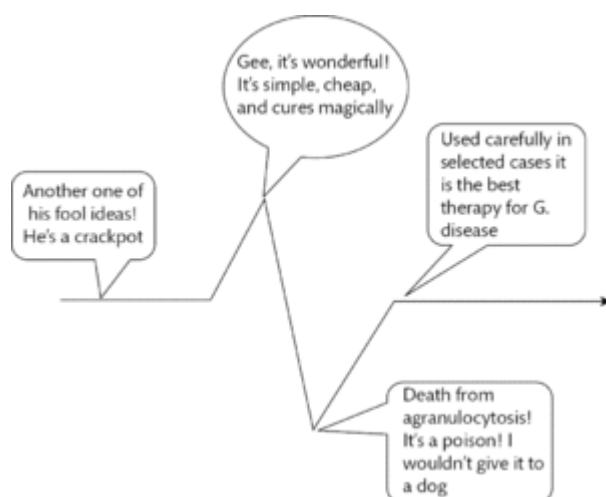


Fig. 57.1
Oscillations in the development of a drug.

Driving is a health-related issue: there is a consistent pattern in many countries around the world of driving cessation relating to illness and loss of function (Campbell et al., 1993; Forrest et al., 1997; Kostyniuk et al., 1998), although driving may persist after other socially useful patterns of mobility have been affected (Hjorthol, 2001). This pattern is reflected in several studies of dementia and driving (Foley et al., 2000). Older people tend not to discuss concerns about driving with healthcare providers (Johnson, 1998): this is a cause of concern as it is possible that remediable medical causes of driving cessation may not be addressed. Lack of access to transportation, and in particular, to driving, is associated with reduced social integration (Mezuk and Rebok, 2008), reduced access to health care (Wallace et al., 2006) as well as earlier

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admission to nursing home care, mortality, and a doubling of depressive symptoms (Marottoli et al., 1997; Chihuri et al., 2016).

Skills and resources needed for assessment of driving

Many professionals working in the psychiatry of old age feel at a loss when confronted with older people who both have psychiatric illness and drive a car. They often do not realize that their many skills used in clinical decision-making also form the basis of making decisions on driving and mobility. These skills are founded in multidisciplinary assessment, and an enabling philosophy and advocacy for older people in the face of nihilism and ageism. In practice, the same skills are seen in the integration of clinical assessment and input from the multidisciplinary team in the calculation of risk in other areas of clinical practice such as deciding on discharge to home from hospital. Elements of the decision-making process for hospital discharge include careful multidisciplinary evaluation, discussion with carers, and perhaps a trial visit home. The elements of that process are very similar to the assessment of fitness to drive. Not only may relatives place security before independence, but as with hospital discharge planning, an approach based on psychometric/cognitive testing is not likely to be helpful. This often surprises clinicians; while psychometric support is important in backing up our diagnostic abilities, it is rarely of help when making decisions about function. For example, the decision that the patient is no longer fit to remain at home and requires placement in a nursing home is much more likely to be taken on the basis of measures of function and behaviour than on psychometric measures.

The premise that the expertise of those who practice psychiatry with older people already contains some of the elements necessary for mobility assessments is not a charter for dilettantism. Rather, it is a challenge to us to develop the extra resources required to ensure that we have adequate support when making decisions about enhancing the safe mobility of older people. This has many parallels with the task of assessing safety at home or capacity to manage financial affairs: in these cases, it is good practice to liaise with an occupational therapist or a neuropsychologist. There has also been a failure to capitalize on the rich level of knowledge of psychiatrists: many of the studies of their practice have been more concerned to highlight their lack of knowledge of the driving regulations rather than to draw on their collected wisdom (Elwood, 1998; Menard et al., 2006; Orr and Elworthy, 2008; Curwen and Jebreel, 2012). It is likely that their estimates of the parameters of safe mobility in their patient groups would have equal, if not greater, validity than current driving regulations restricting driving in psychiatric populations—regulations which are often arbitrary and sometimes counterintuitive and unfair. A helpful addition to this knowledge base is provided by a paper examining the perceptions of psychiatrists and occupational physicians on the minimum period of driving cessation for drivers with psychiatric illness and alcohol dependence (Ryan et al., 2017). That manuscript indicated not only variability in the time

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considered appropriate, but also a tendency to shorter periods off the road than specified in the national guidelines.

At a minimum, the assessment of the impact of psychiatric illness on mobility in later life requires a careful medical and psychiatric assessment, and an informant history (Briggs and O'Neill, 2016). Access to occupational therapy and/or neuropsychology as well as access to a specialist driver assessment is often critical to these assessments, although there are challenges with access and cost (Rapoport et al., 2007; Vrkljan et al., 2013). Given that patients may have medical and psychiatric morbidity, guides for assessing older drivers and those with medical illness have been produced in various countries (Carr et al., 2010; Austroads and National Transport Commission, 2017; Drivers Medical Group/Driver and Vehicle Licensing Agency 2012; Canadian Medical Association, 2017).

There may be a case for developing driver assessment services at a regional level, particularly for those cases where decision-making is not clear after the first assessment. A specific concern relates to the funding of such services. For example, although the mobility/risk problem is clearly health-related in origin, Medicare in the US and Canada will not refund specialist driving assessment and the attendant cost may deter older drivers from seeking help. Similar self-funding challenges exist in other countries with greater or lesser degree of governmental subsidy. The psychiatrist will also need to know the local regulations on fitness to drive and older driver screening, on the obligations of the patient to disclose relevant illnesses to the driver licencing authority and insurance company, and an awareness of the local requirements for physician disclosure, if any.

Assessment of driving behaviour

A model of driving behaviour

Driving is an over-learned skill with a significant behavioural component (Ranney, 1994). The most major advance in this area has been the understanding that a purely cognitive model of driving ability does not adequately reflect the complexity and hierarchical nature of the driving task. We also know that clinicians working with a range of diseases, including dementia, may not accurately predict test road testing ability of drivers (Heikkila et al., 1998; Brown, et al., 2005a; Ranchet et al., 2016a,b). Driver behaviour is complex and one of the simplest and most easily applicable models has been the hierarchy of Michon, which uses strategic, tactical, and operational factors (Michon, 1985). Examples of these levels include: at the strategic level, the choice of whether or not to travel; the tactical decision, e.g. whether or not to overtake; and the operational level, e.g. deciding what to do when overtaking and faced with an oncoming car. Factors at all three of these levels can pose hazards to road safety when impairment exists.

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Multidisciplinary assessment

Box 57.1 shows the most common framework for driver assessment, incorporating the Michon model.

Box 57.1 Framework for driver assessment

History

Patient, family/informant

Driving history

Examination

Functional status

Other illnesses and drugs

Vision

Mental status testing

Diagnostic formulation and prioritization

Disease severity and fluctuations

Remediation

Re-assess

In-depth cognitive/perceptual testing

± On-road Assessment

Overall evaluation of hazard

- Strategic
- Tactical
- Operational

Advice to patient/carer ± driver licensing authority

If driving too hazardous, consider alternative mobility strategies

Not all levels of assessment will be required by all patients: a patient with a homonymous hemianopia is barred from driving throughout the European Union and in most of North America (Carr et al., 2010; Canadian Council of Motor Transport Administrators, 2013), and active planning of alternative transportation is appropriate, including referral to

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a social worker, if available. Equally, a mild cognitive deficit may only require a review by the physician and occupational therapist. The overall interdisciplinary assessment should attempt to provide solutions to both maintaining activities and exploring transport needs. An on-road test may be helpful in more than just the obvious ways: for example, it may demonstrate deficits to a patient or a carer who is ambivalent about the patient stopping driving. At a therapeutic level, members of the team may be able to help the patient come to terms with the losses associated with stopping driving. The occupational therapist may be able to maximize the patient's activities and function and help focus on preserved areas of achievement, while the social worker can advise on alternative methods of transport. This team approach to assessment should save time and offer efficiencies in the assessment process and associated costs for occupational therapy, neuropsychology, and road driver assessors.

Informant history

In addition to the usual work-up, the medical assessment should include a driving history from patient and carer (Iverson et al., 2010). Such informant history may be useful (Brown et al., 2005), especially given clear evidence of the collaborative nature of the driving task among those older people who drive with a regular partner (Vrkljan and Polgar, 2007). Asking about recent crashes is useful, as this can also be supportive information in terms of increased risk, whether through pre-morbid 'risky' behaviour (Fuller, 1992) or the effects of age-related disease (Daigneault et al., 2002). Caregiver concern about driving ability, in particular, is a challenging area for clinicians. A history of recent crashes has been recommended as an important consideration and marker for the need for driving, but the absence of any recent collisions is considered less predictive or helpful (Iverson et al., 2010). Caregiver concerns were associated with road-test outcomes in two recent studies of cognitively impaired drivers (Bixby et al., 2015; Hemmy et al., 2016). However, in one of those studies the caregiver concerns were only correlated with on-road and naturalistic driving outcomes when the caregiver was an adult child (mostly female in that study), but when the caregiver was a spouse (mostly male), better ratings of driving ability were counter-intuitively associated with worse driving performance (Bixby et al., 2015).

Cognitive screening tests

The relatively poor clinical utility of cognitive scales in determining fitness to drive (Molnar et al., 2006a) relates to their lack of congruity to current models of driving behaviour and capabilities (Fuller, 2005). This does not mean that cognition should not be assessed, but rather that such measures should be integrated with other factors in the comprehensive assessment, including an assessment of insight/anosognosia, judgment skills, and strategic thinking. The Mini-Mental State Examination (MMSE) (Folstein et al., 1975) was one of the first simple screening measures of cognitive impairment reviewed in terms of driving and dementia and illustrates the challenge of over-reliance on such instruments. A

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attempted consensus exercise suggested that those who score 17 or less on MMSE require further assessment in a formal way (Lundberg et al., 1997). The choice of cut-off at a relatively low score reflected unease among the participants that reliance on a simple test such as the MMSE would over-simplify the complex task of appropriate assessment of older people with dementia.

The next stage of testing described in the literature has been performed mainly by occupational therapists and neuropsychologists. None of the studies has been sufficiently large to have a reasonable predictive value or to determine cut-off points on neuropsychological test batteries. This situation is parallel to that in memory clinics where there is a wide variation in the test batteries used. It is likely that the important elements of successful assessment that assist in discriminating safe from unsafe drivers are the choice of key domains, familiarity with a test battery, and the development of an understanding and close liaison between the physician and the occupational therapist and/or neuropsychologist.

Specific tests which show some degree of correlation with driving ability in more than one study (Mathias and Lucas, 2009) include the MMSE, the Trail Making Test (Maag, 1984; Janke and Eberhard, 1998; Mazer et al., 1998; Stutts, 1998); and a range of tests of visual attention (Klavora et al., 1995; Duchek et al., 1998; Marottoli et al., 1998; Owsley et al., 1998; Trobe, 1998), including the Useful Field of View®, (a composite measure of pre-attentive processing, incorporating speed of visual information processing, ability to ignore distractors (selective attention) and ability to divide attention; Ball et al., 1991), and the Driving Scenes Test of the Neuropsychological Assessment Battery (Brown et al., 2005b). Several other tests have been assessed in single studies, including traffic sign recognition (Carr et al., 1991).

Overall, numerous detailed neuropsychological tests have been correlated with driving behaviour but few are sufficiently robust to calculate cut-off points for risky driving (Molnar et al., 2006a; Hird et al., 2016). More recent studies of other frequently used cognitive screening instruments, the Montreal Cognitive Assessment (MoCA) and the Clock Drawing Test to be only modestly predictive of on-road performance in samples of older adults (Manning et al., 2014; Hollis et al., 2015). All of these tests can be criticized for taking an overcognitive view of the driving task, an excessively circumscribed concept of the breadth of cognitive function and a failure to incorporate the cognitive gains of later life in tandem with the losses (O'Neill, 2012). Reviews of this topic are available from the US National Highway Transportation Safety Administration (Staplin et al., 1999) and elsewhere (Reger et al., 2004; Molnar et al., 2006a; Bennett et al., 2016; Hird et al., 2016).

In conjunction with the clinical assessment and collateral history, these tests will help to decide which patients require on-road testing, as well as those who are likely to be too dangerous to test on-road.

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Role of on-road testing

On-road driver testing is generally considered the gold standard and should be offered to all patients in whom there is uncertainty about driving skills, as long as they are not clearly dangerous when driving and not disqualified from driving for other reasons, e.g. homonymous hemianopia or convulsions. At least three different road tests have been tested empirically, but the sample sizes of the studies have been relatively small (Fitten et al., 1995; Hunt et al., 1997; Dobbs et al., 1998). Furthermore, although one study reported a fairly acceptable one-month test-retest reliability of 0.76 for one of these road tests (Hunt et al., 1997), other data on reliability of these tests are lacking for this supposedly gold-standard. From the point of view of external and predictive validity, many driving errors on these tests may represent normative changes with age (Selander et al., 2011), and data is lacking correlating on-road test with actual driving, because of ethical limitations of allowing those who fail to continue driving.

Dementia

Our recent systematic review of studies published from 2005 to 2015 found only two studies comparing motor vehicle crashes (MVCs) in patients with dementia to a healthy comparison group without dementia (Chee et al., 2017). One study showed that drivers with a diagnosis of dementia had more than a fourfold increase in risk of collisions per 1,000 miles driven in their retrospective analysis at baseline, but during the three-year prospective study period 11% of normal controls had a collision compared to only 1% of drivers with dementia—a difference that was not, however, statistically significant when corrected for the number of miles actually driven (Ott et al., 2008). The other study identified showed no statistically significant increase in MVCs over the same time span (Davis et al., 2012). A prior systematic review incorporating studies published from 1996 to 2006 found that all three identified retrospective studies using informant-reported collision risk consistently found greater collision risks among patients with dementia than controls, but studies were much more variable when considering only official state-recorded collisions—only one of three of these studies was positive (Man-Son-Hing et al., 2007).

In contrast, our more recent systematic review (Chee et al., 2017) found robust medium to large effects of dementia on driving abilities in six of the seven identified studies that examined driving impairment comparing with healthy controls. Furthermore, in that review, a meta-analysis of four identified studies, those with dementia were much more likely to fail a road test than healthy controls (RR 10.77, 95% CI 3.00–38.62, $z = 3.65$, $p < 0.001$). Thus, determining the risk of collisions in people with cognitive impairment or dementia remains elusive, largely because of challenges in recruiting patients for such studies and of measuring exposure to driving. The very limited body of literature, mostly based on proxy reporting,

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shows conflicting results, in contrast to compelling and consistent evidence of deterioration in driving skills.

Even though there are difficulties establishing an increased risk of collision specifically associated with dementia relative to controls without dementia, at a population level such events are not rare in the community. In a cohort of 210,550 patients with dementia observed from 1997 to 2005 in Ontario, Canada, 40,508 (19.2%) had active driver's licenses (Rapoport et al., 2008). Of those with active licenses, almost one-quarter (24.1%) were involved in a collision, and in the vast majority (77.9%) of these, the crashes occurred before the diagnosis of dementia (defined in that particular study by a prescription for a cholinesterase inhibitor). In that sample, the patients had been deemed at fault for more than half of the collisions, and personal injury occurred in almost a quarter of cases. When patients with dementia drive, they continue to do so for a long time (Herrmann et al., 2006), even while their driving deteriorates (Duchek et al., 2003), potentially posing concerns for safety over time. However, drivers in Quebec who were registered as affected by dementia had a lower crash rate than the population average (Dow et al., 2013).

The Canadian Medical Association Driver's Guide suggest a trichotomized approach, based on opinion and heuristics, rather than evidence (Canadian Medical Association, 2017). The physician is asked to consider the answer to four questions based on the results of their assessment:

1. Would I get into a car with the patient driving?
2. Would I let a loved one get into a car with the patient driving?
3. Would I want to be crossing the street in front of a car with the patient driving?
4. Would I want to have a loved one cross the street in front of a car with the patient driving?

For each question, three answers are possible: 'yes' (meaning there are no concerns that would trigger further testing), 'uncertain' (meaning that more tests are required), and 'no' (meaning that the risk is clear and too high). This approach can be critiqued for potential bias relating to negative misperceptions about older drivers and ideally should be assessed as to its utility in further studies.

Although most people with progressive illnesses such as the dementias will eventually undergo decline function and behaviour, it is not clear to what extent this poses a public health risk from a driving perspective (Carr and Ott, 2010). It is more likely that the process of reducing mileage and eventual withdrawal from driving protects the general public from the harmful effects of the illness on driving safety (Trope et al., 1996; Carr et al., 2000). Reassuringly, the process of self-regulation in terms of reduced mileage is also apparent with mild cognitive impairment (O'Connor et al., 2010). Indeed, focus groups of those with Alzheimer's disease, their caregivers and professionals were almost unanimous in saying that, with self-regulation, those with mild AD should continue to

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drive (Perkinson et al., 2005). Nonetheless, clinicians and patients should agree on a follow-up schedule for review of deterioration of their clinical status to the point that driving skills may become unsafe which is congruent with practice in their jurisdiction.

Other psychiatric illnesses

The role and impact of illnesses in older age on driving other than dementia has been even less widely studied, apart from alcohol dependency. The overall impression from the literature is that the added risk from schizophrenia and affective disorders is small (Marshall, 2008), although the issue is complicated by the use of psychoactive medications (Soyka et al., 2005). The emphasis on risk rather than on mobility is similar to the rest of the field, and it is likely that those with psychiatric illness have less mobility than the population as a whole. In an early study, Buttigliere and Guenette (1967) found that subjects with psychiatric illness had accident and violation records similar to the general population. Patients with schizophrenia and depot neuroleptics show a worse driving performance on a driving test than unmedicated healthy controls (Wylie et al., 1993), but concrete evidence of increased crash risk is not available. A Swiss study (Sacher, 1978) of mostly young and middle-aged people with schizophrenia showed more violations and accidents in those with delusions of a religious type, but fewer accidents or violations among those with a 'cautious, anxious character'.

Even more recent studies of driving in patients with psychiatric illness, although mostly not older adults, have been limited by the use of psychomotor and cognitive tests as proxies for driving, in the absence of tests of actual driving (De Las Cuevas and Sanz, 2008; Segmiller et al., 2013). An observational study in Australia (Berecki-Gisolf et al., 2015) found that of 743 drivers who were injured in a non-fatal motor vehicle collision, 12% had used antidepressants in the year prior to the injury, and the authors concluded that less than half of antidepressant use after injury could be attributable to the injury itself. However, it should be noted that only one quarter of their sample was aged 65 years and over, and no conclusions could be made about the risk of collision associated with these antidepressants. In a study of older adults in Ontario (Rapoport et al., 2011), 5% of 159,678 individuals who had a motor vehicle collision between 2000 and 2007 had received an antidepressant in the month prior to the collision. Although the risk of collision associated with a second-generation antidepressant (SSRIs and newer agents) was modestly increased (HR 1.10, 95% confidence interval 1.07–1.13, $p < 0.0001$), this association was restricted to those who were prescribed a benzodiazepine or strong anticholinergic medication concurrently with the antidepressant, and was restricted to the first three to four months after the antidepressant was prescribed.

The use of car crashes as a means of suicide is considered to occur in a very small proportion of crashes, despite a suggestion from early studies that this might be a more marked problem. Subsequent studies have

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shown the risk to be quite small (Tabachnik et al., 1966; Schmidt et al., 1977; Isherwood et al., 1982), including a recent survey reported in abstract form of 16 US states from 2005 to 2011 in which only 1% of violent suicides were categorized as suicides by motor vehicle. The authors note that those who completed suicide by motor vehicle were younger than those who died by other methods of suicide, and were predominantly white, male, and under the age of 55. About one-third of the suicide-by-car sample tested positive for alcohol, and one-third had a current mental health problem at the time of their death, although only a quarter were receiving treatment for this (Sung, 2017).

So where does this leave the clinician in this area? Key considerations are likely to be the severity and stability of the patient's condition, their insight, impulsiveness, and their ability to appropriately engage with the strategic, tactical, and operational elements of driving to prevent and avoid road hazards, as well as clarifying that there are no suicidal plans which, in this context, might involve a vehicle (Canadian Medical Association, 2017). Ideally, adverse effects of medications will be minimized, with due caution with the use of sedating antipsychotics or long-acting benzodiazepines.

Medications

An area of increasing debate over the last 25 years has been the potential impact of psychoactive medications on driver safety. This interest has paralleled studies showing an impact of these medications on increasing the risk of other injuries (Ray et al., 1992), notably falls. A number of studies have suggested that physicians should be concerned about diminished driving skills and increased crash risk with psychoactive medications (Ray et al., 1993; Hemmelgarn et al., 1997). In terms of numbers of prescriptions, the main groups implicated are the benzodiazepines (Hemmelgarn et al., 1997) and antidepressants (Ray et al., 1992). If a true increased risk can be established and quantified, by medication type and dosage, restrictions either in prescribing or on driving (or both) may be an achievable component of a crash-prevention strategy.

Demonstrating cause and effect has been problematic. Separating the effects of the disease from those of the medications is not easy: depression, anxiety, and insomnia may have an impact on driving behaviour that might be ameliorated by pharmacological treatment. Studies on volunteers do not replicate clinical experience. There is significant research that has examined reaction time, braking time, and deviation of lateral position in relation to psychoactive medications using simulators or on the road testing (Rapoport and Banina, 2007; Verster and Roth, 2011, 2012) but there is a relative absence of research into the impact of medications on the strategic and tactical elements of driving.

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A parallel here is to consider the theoretical differences between tricyclic anti-depressants (TCAs) and selective serotoninergic reuptake inhibitors (SSRIs) in relation to the risk of falls. Although SSRIs would seem to have theoretical advantages, clinical studies have not been able to show any difference in fall rates between older people on TCAs or SSRIs (Thapa et al., 1998). In the study described previously of antidepressants and crashes in older adults in Ontario, the observed modest risk of crash associated with second-generation antidepressants was not at all observed with first generation antidepressants such as tricyclics and monoamine oxidase inhibitors (Rapoport et al., 2011). Epidemiological studies of car crashes often have shortcomings, such as how they match controls with cases, in the exclusion of fatalities (which are more likely to involve alcohol and possibly psychoactive drugs), unreliability in medication recall at interview, lack of valid diagnostic categorization prior to the crash, and failure to control for the many variables that affect crash risk.

We conducted a systematic review of the literature from 1946 to 2013 pertaining to antidepressants and driving in older adults (Cameron and Rapoport, 2016). We found only one experimental study on this topic, which found imipramine to have detrimental effects on highway driving, whereas nefazodone (an antidepressant that has largely been discontinued) did not, although this was not a study of depressed older adults. Seven of eight identified population-based studies reported a significant increased risk of involvement in a collision associated with antidepressant use. However, these studies had significant limitations, including lack of reporting on dose and duration of the drug, lack of information of driving exposure, lack of adjustment for confounders such as other medication use, lack of ascertainment of at-fault status, and generally a lack of distinction between classes of antidepressants, let alone individual agents.

A meta-analysis of 11 epidemiologic and 16 experimental studies showed an association between benzodiazepines and MVCs in six case-control studies (OR 1.61, 95% CI 1.21–2.13), and in three cohort studies (OR 1.60, 95% CI 1.29–1.97) (Rapoport et al., 2009). The heterogeneity in the analysis was reduced when restricting to the three case-control studies and two cohort studies involving older adults, although the magnitude of the association was somewhat attenuated. The newer class of sedatives, Z-drugs, such as zopiclone and zolpidem, may be no safer (although there have been no head-to-head comparisons to date with respect to driving safety); there was generally an increased risk of collision associated with these drugs in recent studies, mostly case-crossover design in which patients serve as their own controls. Such a design eliminates the problem of comparing patients with dissimilar controls. Zolpidem was associated with an increased collision risk in four recent studies (Gustavsen et al., 2008; Gibson et al., 2009; Yang et al., 2011; Orriols et al., 2011), of which only two included older adults (Orriols et al., 2011; Yang et al., 2011). Zopiclone was associated with collision in three recent

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studies (Barbone et al., 1998; Gustavsen et al., 2008; Gibson et al., 2009), but not in two others (Orriols et al., 2011; Yang et al., 2011). Only one of the three positive studies of zopiclone included older adults (Barbone et al., 1998), and both of the negative studies included older adults. The magnitude of effects of these studies was variable.

Universal advice against driving while taking benzodiazepines and Z-drugs is not yet supported by these studies, but it should accelerate both epidemiological and policy interest in the subject, as well as clinical caution. Those who prescribe benzodiazepines and Z-drugs need to recognize that most adult patients are drivers or potential drivers. Active consideration should be given as to whether the illness is likely to affect driving skills and whether the patient has a past crash history. The patient should be advised not to drive if they cannot abstain from alcohol while on treatment with benzodiazepines. Most importantly, the prescriber should query whether the patient really needs a benzodiazepine, and if they do, whether it needs to be long acting, as the longer-acting benzodiazepines are more closely associated with collisions (Hemmelgarn et al., 1997; Rapoport et al., 2009).

Practical guidelines

In advising a patient who is also a driver, the psychiatrist must first ask how the patient's illness affects their mobility. A secondary goal is to assess the potential safety risk. The considerations outlined in Box 57.1 should be assessed, and ideally any longer-term decisions on driving should be made when the patient's condition is stabilized and optimized. An interim decision will have to be made until the assessment is completed, and this may involve asking the patient to desist from driving temporarily. Some countries have reasonably well-developed schemata for helping clinicians and, increasingly, they have recognized the value of specialist opinion. For example, the 'At-a-Glance' leaflets from the UK driver licencing authorities (<http://www.dvla.gov.uk/media/pdf/medical/aagv1.pdf>) have moved on from an assumption that hospitalization is the norm for significant psychiatric illness, to a model based more on ambulatory care, with reference made to specialist opinion. Some of the driver licensing authorities' criteria also seem unnecessarily strict and, as the field of driver assessment matures, it will be important that professional organizations make representations to driver licensing authorities to ensure that the regulations are fair. Guidelines from the Association for the Advancement of Automotive Medicine stress the importance of leaving many of the decisions to the specialist, assuming appropriate assessment back-up (Dobbs, 2002). The quality of clinical practice guidelines on assessing drivers with medical illness has been recently criticized for limitations in rigour, stakeholder involvement, and applicability (Rapoport et al., 2015), and efforts to improve these are being made. In the interim, physicians who feel that the regulations hinder the health, wellbeing, and mobility of their patient unnecessarily may need to consult their medical defence organization about the clash of

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ethical responsibilities that they may feel toward to both their patient and others.

In some cases, it may be apparent that there are no concerns about driving safety or, conversely, that the patient is too unstable or compromised to drive safely. In cases where the judgment lies in between, a full assessment including an on-road driving test may be required. Once a decision has been made, the psychiatrist needs to inform the patient of their responsibility to report to the local driver licensing authorities and/or their insurance company: this discussion should be documented in the clinical notes. We tend to phrase this by suggesting to the patient that they review their insurance policy documentation. Patients' responsibilities vary enormously from jurisdiction to jurisdiction. Failure to inform the patient of the relevant requirement may expose the doctor to criticism or even litigation. The psychiatrist also needs to be aware of any statutory requirements for physicians to report illnesses such as dementia to driver licensing authorities, as is the case in California and most Canadian provinces. Reporting a driver when one lacks confidence that there will be a fair and sensitive assessment by the driver licensing authority can pose an ethical dilemma. It is also notable that living in a jurisdiction with mandatory reporting does not appear to have an impact on driving cessation in Alzheimer's disease (Herrmann et al., 2006), raising a question over the usefulness of mandatory reporting, which may have the unintended effect of deterring patients with dementia from seeking care from their physician. In a jurisdiction with mandatory reporting legislation, there was considerable variability between physicians (mostly geriatric psychiatrists and geriatricians) in the frequency with which hypothetical cases with mild dementia and mild cognitive were reported to the transportation authorities (Rapoport et al., 2014b). Although clinical variables such as caregiver concern and cognitive performance were predictors of whether reports were submitted, physician-related factors, such as male gender and a tendency to experience stress from having to deal with areas of medical uncertainty, also increased physician reporting (Rapoport et al., 2014a).

If the assessment points to safe driving practice, the decision to allow continued driving entails several further judgments on the part of the doctor. These are:

1. Interval before review
2. Possible restriction
3. Driving accompanied
4. Licencing authority reporting relationship in the jurisdiction
5. Insurance reporting responsibility i.e. doctor or patient.

Since dementia is a progressive illness and affective disorders and alcohol dependency are recurrent or relapsing diseases, it is prudent to make any declaration of fitness to drive subject to regular review. For dementia, our own practice is to review again in six months, or sooner if

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any deterioration is reported by the carer (Breen et al., 2007). Some support is given for this approach in one of the longitudinal studies of driving and dementia (Duchek et al., 2003) and in a systematic review (Molnar et al., 2006b). Following evidence that the crash rate is reduced if the driver is accompanied (Bédard et al., 1996), it could be sensible to advise the patient to driving only when there is someone else in the car, using the accompanied driver paradigm (Shua-Haim and Gross, 1996). Although the phrase 'co-pilot' has been used in the literature for accompanied driving, this might imply participation in the driving process, as opposed to presence and observation, and thus 'accompanied driving' represents a better description. There is also preliminary evidence from the state of Utah that those drivers with restricted driving licences have lower crash rates (Vernon et al., 2002), and this is almost certainly an under-utilized strategy (Langford and Koppel, 2011), although the use of this strategy among patients with psychiatric illness has not been evaluated. Patients should be advised to avoid traffic congestion as well as driving at night and in bad weather. Nonetheless, empirical evidence supporting accompanied driving and driving restrictions among patients with psychiatric conditions including dementia are lacking. The patient and carers should be advised to acquaint themselves with local driver licensing authority requirements as well as the policy of their motor insurance company. All of these should be clearly recorded in the medical notes.

Supporting cessation

How do older drivers with dementia deal with driving cessation when driving is no longer possible?

There is strong evidence that most drivers with dementia not only limit their own driving and cease driving voluntarily (Foley et al., 2000) but also are amenable to pressure from family and physicians. In one of the largest studies 18% stopped driving of their own accord, 23% because of physician advice, 42% because of family members, and the rest by a combination of interventions (Trope et al., 1996). In a recent study, factors predictive of driving cessation included global deterioration, lower level of cognition (Talbot et al., 2005), and some interesting trends on neuropsychiatric behaviour; agitation made it less likely that a patient would cease driving, whereas apathy and hallucinations made it more likely (Herrmann et al., 2006). Living in rural areas is associated with later cessation of driving (Talbot et al., 2005). There are no studies of how patients with dementia compensate for the loss of independent transport mobility afforded by driving that is needed to fulfil their social, occupational, and health needs, and considerable concern exists that these needs are not met adequately (Taylor and Tripodes, 2001). However, psychological adaptation to driving cessation may be helped by diagnosis and psychotherapeutic input (Bahro et al., 1995).

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There have, however, been very few controlled studies assessing the impact of interventions aimed at supporting driving cessation among older adults. In a recent systematic review (Rapoport et al., 2017), we identified three such studies—one was described an intervention for retired drivers with dementia, another was aimed at caregivers of drivers with dementia, and the third included retired and retiring drivers without dementia. The study of retired drivers incorporated a 16-week group based programme with problem- and emotion-focused coping strategies, and reported a significant effect on depressive symptoms compared with a traditional support group (Dobbs et al., 2009). The study of caregivers involved a four-week programme of two-hour group educational sessions and reported significant effects on self-efficacy, acceptance, and preparedness for change compared with two control groups—a waiting list and those given written materials only (Stern et al., 2008). In the study of older adults without dementia, six weekly group sessions of education and support increased their reported episodes of getting out of the home relative to a waiting list control (Liddle et al., 2014). These studies provide promising approaches toward supporting older drivers through the cessation process, although they are limited by their use of subjective ratings.

In the meantime, what should doctors advise for those patients they assess as unfit to drive? If the assessment supports driving cessation, patients and carers should be advised of this, and a social worker consulted to help maximize transportation alternatives (Windsor and Anstey, 2006). Giving up driving can have a considerable effect on lifestyle. Healthy older drivers accept that their physician's advice can be very influential in helping them decide to give up driving (Rabbitt et al., 1996).

The way we deal with driving reflects how we help the patient to deal with the reality of the deficits caused by dementia or other psychiatric illnesses. If the positive and collaborative approach described is not successful, confidentiality may have to be broken for a small minority of cases. Most professional associations for physicians accept that the principle of confidentiality is covered to a degree by a 'common good' principle of protecting third parties when direct advice to the patient is ignored (American Medical Association, 1999). Removal of the driving licence is not likely to have much effect on these patients, and the vehicle may need to be disabled (Donnelly and Karlinsky, 1990) and all local repair services warned not to respond to calls from the patient. In such cases, medicolegal advice should be sought from the malpractice organization before breaching confidentiality, and such actions should be in alignment with local healthcare policies.

In the event of a decision to advise cessation of driving, advice from a medical social worker may be helpful in planning strategies for using alternative modes of travel. This may be particularly difficult in rural settings: the political system has not woken up to the need for adequate paratransit, i.e. tailored, affordable, and reliable assisted transport that is

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acceptable to older adults with physical and/or mental disability (Freund, 2000). Tailored transport (paratransit) is expensive, but there are imaginative social economy models (such as ITNAmerica.org) that have shown promise (Freund, 2007), and may ultimately be found to have benefits in reducing institutionalization and in improving quality of life.

Screening for dementia among older drivers

Despite the lack of convincing evidence for an older driver 'problem', ageist policies in many jurisdictions have led to screening programmes for older drivers. In the absence of reliable and sensitive assessment tools and this approach is flawed, as illustrated by data from Scandinavia (Hakamies-Blomqvist et al., 1996). Finland had regular age-related medical certification of fitness to drive, whereas Sweden had no routine medical involvement in licence renewal. The number of older people dying in car crashes in Finland was no less than in Sweden but the number of those dying as pedestrians and cyclists was higher, possibly, in part due to the fact that drivers were unnecessarily removed from their cars. Equally, in Australia, the state with the lowest number of crashes among older drivers was the one that did not undertake age-based medical screening of older drivers (Langford et al., 2004). Adding a cognitive screening test to a population medical screening programme in Denmark was shown also to have no effect upon in-car mortality, but instead appears to increase the deaths among older road users, suggesting that screening shifted older persons from driving to less safe modes of transportation (Siren and Meng, 2012).

A more minimalist and less medical approach using very simple measures, such as a vision test and a written skill examination may be more helpful (Levy et al., 1995): unfortunately this approach is also associated with a reduction in the number of older drivers, and thus has a possible negative health impact, given the extensive literature of the negative impacts of driving cessation (Levy, 1995). Another approach is opportunistic health screening, for example, those older drivers with traffic violations (Johansson et al., 1996). It remains to be seen whether these and other screening policies reduce mobility among older people, which is a practical and civil rights issue of great importance.

Conclusions

There are numerous challenges for the psychiatrist assessing older adults who drive. All psychiatric conditions have the potential to impair driving, but, conversely, there are other older adults with the same conditions whose driving does not seem to be impaired. Predicting who is and who is not impaired is quite difficult, as physicians simply do not have the capacity for direct observation of their patients' driving. Most older adults who drive rely on their vehicle for autonomy and social engagement, and withdrawal of driving privileges can lead to adverse psychosocial consequences and worsening of their psychiatric condition, even when cessation is necessary for public and patient safety. The

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situation is further frustrated by a lack of empirical evidence of the magnitude of the true risks of the psychiatric conditions and their treatments, evidence for interventions to support community mobility and life-space of older adults planning driving cessation and beyond cessation, and rigorous clinical practice guidelines. We have advocated in this chapter for a practical approach that makes use of a multidisciplinary team and a destigmatizing of the older driver and the driver with psychiatric illness. We have emphasized the precarious balance of safety and autonomy, a considered consultation with collateral informants, a judicious understanding of local legislation, and red flags that may highlight a problem with driving ability. This should be coupled with an emphasis on providing psychosocial and psychiatric support for older adults in planning for driving cessation, and for maintaining community mobility after they have stopped driving.

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The law relating to mental capacity and mental health

Chapter: The law relating to mental capacity and mental health

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Introduction

The law discussed in this chapter is primarily the law of England and Wales, but there are many parallels between the law discussed here and other jurisdictions. By way of illustration, the jurisdictions of the US, Canada, Australia, New Zealand, South Africa, and the countries of South Asia are all based upon the English common law. For example, the concept of 'necessity' is a common law concept that was used prior to the Mental Capacity Act to justify non-consensual treatment in certain circumstances, and this will be available in those common law jurisdictions lacking specific legislation relating to capacity.

Prior to the passing of the Mental Capacity Act 2005, there were no statutory provisions relating specifically to decision-making capacity. Persons who did not have capacity were treated in their best interests based upon the common law doctrine of necessity. It is this doctrine that had enabled doctors to lawfully treat unconscious patients, i.e. those with

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temporary lack of capacity, and it was further developed so that it could be used to treat persons permanently lacking in capacity, such as people with dementia. Furthermore, the power of the original Court of Protection had only been statutorily defined in relation to dealing with the property of the person lacking capacity. This lacuna and other concerns gave rise to a Law Commission Consultation Paper and Report, and a number of government papers. The Mental Capacity Act was passed in 2005. Significantly, the original proposal was for a Mental Incapacity Act, but this was changed to emphasize what has become a presumption in favour of a person having capacity.

However, before we move on to the Mental Capacity Act, it is appropriate to consider a particular aspect of capacity law that has been considered by the courts since the nineteenth century.

Testamentary capacity

This is something that is particularly relevant to older people. If a will is not valid, due to a number of reasons, one of which is testamentary incapacity, then either the law of intestacy will apply, or an earlier valid will remains the applicable instrument. In the case of *Burns v Burns* [2016] EWCA Civ, 37, the Court of Appeal had to consider an appeal from a decision of the High Court that a will made in 2005 was valid. As is usually the case in this type of litigation, the matter had come before the court because of a dispute between the beneficiaries following the death in 2010 of the testator at age 89. In 2004 she had undergone a number of assessments, and was diagnosed as suffering from moderate to severe depression. The issue before the Court of Appeal was whether the judge was entitled to form his conclusion on the medical and other evidence before him. The first of the medical evidence was a Mini-Mental State Examination (MMSE) carried out in 2003 by a community psychiatric nurse where the testator scored 19 out of 30, with her main shortcomings being in memory assessment and orientation/awareness of the current circumstances such as date, season, etc., and failing to recall objects mentioned to her earlier by the nurse. The second evidence was given by the manager of her care home; this evidence was found to be inconclusive on the basis that her mental state may well have been different in 2004 from 2010 when she died (the manager had known her during this period, but conceded this point). A subsequent occupational therapy assessment, carried out in 2005, had concluded that the testator had moderate impairment and a medium level of dependency. The Court of Appeal held that the judge in the High Court had been entitled to find that she had capacity and knew and approved the contents of her will, despite the evidence that there was some mental impairment at the time.

The judge referred to the 'golden rule', which essentially is not a rule of law but guidance to a lawyer dealing with a testator whose capacity may be in doubt, and which, as confirmed in the case of *Buckenham v Dickenson* [2000] WTLR, states that the lawyer should have prior knowledge of the testator, should consider whether the will should be

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witnessed by an approved medical practitioner, and that the proposed will should be considered in the context of any earlier will, and making sure that the reading through of the will is not 'an idle ceremony'. Despite impairment, the judge decided, on the basis of the case of *Parker v Felgate* [1883] 8PD 171, that she knew she was signing a will and that she was aware of her assets. It was described as a 'simple will'. There was much discussion about the judge's conclusions, but the Court of Appeal found that the judgment was not unsound, given that the judge had heard all the evidence and had taken into consideration the applicable law.

Looking back at the assessments in *Burns*, and, for example, the poor scores on orientation, it is interesting to consider the case of *Simon v Byford* [2014 EWCA Civ 280, another Court of Appeal case, where it had been held that capacity was about understanding and not a test of memory.

It is worth noting here that statutory wills can be authorized by the Court of Protection. An example is the case of *Re J (A Protected Party)* [2016] EWCOP 52, where it was held that it was in the best interests of an elderly woman suffering from dementia for a statutory will to be executed on her behalf, whereby her estate was to be left in unequal shares to her two sons. This was based upon her past and present wishes and matters that she would have taken into account if she had capacity.

The Mental Capacity Act 2005 (MCA)

The MCA applies to everyone over the age of 16, but, of course, has a particular application to older people because of the potential for them losing capacity being greater than that of the general population. Prior to the enactment of the MCA, there were powers vested in the Court of Protection that enabled the property of those without capacity to be managed, but there were no provisions to cover personal welfare matters. These were dealt with by the inherent jurisdiction of the courts under the common law. The key change made by the MCA is that it remedies this gap and the Court of Protection now has power to make welfare decisions, as well as property, etc.

Having said that, the provisions of the MCA do not add a great deal to the common law, but for non-lawyers it is more accessible, and there are useful additions, embellishments, and clarifications. For example, there are five principles contained within section 1 of the MCA: a presumption of capacity until established otherwise; all practical steps must have been taken to help a person make a decision before concluding that he lacks capacity; unwise decisions are not to be taken as evidence of lack of capacity; any act done or decision made in respect of someone without capacity must be in his best interests; and an act or decision must be arrived at after due consideration has been given to achieving least restrictive and the person's rights and freedom of action.

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People lacking capacity

The law takes a functional approach, i.e. it depends upon the nature of the decision to be made as to whether a person has capacity. There is a tendency to think in terms of life and death decisions, partly because these are the most serious, and partly because it is in that area that most of the court applications lie. However, the same principles apply to decisions of everyday life (e.g. what does this person want to wear, to eat) and clearly the capacity to make such decisions is present in all but the most seriously disabled people. There is also a tendency to think in terms of medical care and treatment because of their almost unique quality of invading bodily integrity. However, many other personal welfare decisions can be equally serious, in particular, the decisions as to where and with whom one lives.

The functional approach is illustrated well by the case of *London Borough of Southwark v (1)KA (2)MA (3)RN* [2016] EWCOP 20. K, aged 29, had learning disabilities. He lived with his family and could not manage without that support and the support of a day centre. His family were hoping to find a wife for him. The local authority obtained forced marriage protection orders and applied to the Court of Protection for a declaration that he did not have the capacity to litigate, make personal welfare decisions, and decisions about sexual relations and marriage. The court found that he lacked capacity only in respect of litigation. He understood about marriage, sex, and pregnancy, and he understood his basic care and health needs, the role of a doctor, and the need to take medical advice. He did not understand the law or why his circumstances should come before the court and therefore he could not litigate unaided.

Section 2 of the MCA states that, in order to come within the ambit of the legislation, a person will only lack capacity if it is because of 'an impairment of, or a disturbance in the functioning of, the mind or brain'. It can be permanent or temporary and incapacity cannot be established merely by reference to age or appearance or behavioural traits, something particularly to be kept in mind when dealing with older people. In section 3, it states that a person lacks capacity if he is unable to: understand the information relevant to the decision; retain that information; use or weigh up the information to make the decision; or communicate the decision. This is almost the test used in the case of *Re C (Adult: Refusal of Treatment)* (1994) 1 WLR 290, where there was no reference to communication, but an additional requirement was imposed by the court: the patient must believe the information. The problem with this requirement is that a patient's beliefs can be irrelevant. This is illustrated by the facts of that case. The patient was told that without the treatment he did not want he had an 85% chance of dying. In such circumstances, a patient might not believe what he was being told, despite factual evidence to the contrary, and this might be because he believes the doctors are lying to him. In such a case, this might mean that he does not have capacity. On the other hand, he could genuinely believe that he fell into the 15% of people who would not die. In other words, the

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question of belief is not helpful in deciding on capacity. In any event, this aspect of the judgment was not imported into the MCA.

Information relevant to the decision includes information about the consequences of deciding in one way or another, or of failing to make a decision at all, and the information has to be communicated to the person in the most appropriate way, e.g. by the use of simple language or visual aids. Retention of the information only has to be for a short period of time. The language is certainly very open-textured, although assistance may be obtained from the MCA Code of Practice (Department of Constitutional Affairs, 2007).

The MCA is more likely to be applicable in the case of older people than the Mental Health Act 1983 (MHA), as their mental disorder is more likely to be some form of dementia leading to lack of capacity, whereas many disorders, such as bipolar disorder, often affecting a much younger population, do not necessarily affect capacity.

Best interests

Again, the language of section 4 that deals with best interests is very general, as it has to be, but the devil is in the detail of the application of the section to a particular case. The MCA Code of Practice provides guidance on this, stressing the importance of the caveat that age, appearance, and behaviour are not relevant factors in capacity law, and they should not be used in deciding what is in a person's best interests. There is also a requirement to consider whether the person concerned will regain capacity. This could be important in cases where an older patient is, for example, confused as the result of an acute infection. Insofar as is reasonably practicable, the person must be permitted, and indeed encouraged, to participate in any act done for him and any decision affecting him, and the person's past and present wishes, feelings, beliefs, and values must be taken into account and, in particular, any relevant written statement made when the person had capacity. Where appropriate, the views of others must be taken into account. Curiously, section 4(5) states that '[w]here the determination relates to life-sustaining treatment he must not, in considering whether the treatment is in the best interests of the person concerned, be motivated by a desire to bring about his death', and one is tempted to say that we are all highly relieved to know this. The provision was inserted as a result of concerns expressed by the anti-euthanasia lobby. Interestingly, it has been held by the House of Lords that it is possible to sanction a procedure on the basis that it is not against the interests of the person concerned. This was in the case of *S v S* (1972) AC 24 and is prior to the enactment of the Mental Capacity Act. It concerned an application to the court for an order that a blood sample be taken from a child in order to establish paternity, and it was said that this would not be against the interests of the child and the appropriate order was made.

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By way of a comparative illustration, in the US the concept of 'substituted judgment' is favoured as a test for the validity of decisions made in incapacity cases. This means that the decision is based upon what the person would have wanted if he had capacity (Weber, 1985). This was canvassed in the House of Lords case of *Airedale National Health Service Trust v Bland* (1993) AC 789, and rejected by the court, and arguably the court was right, on the basis that it was too narrow a test. After all, a person's views might not have been known, or he may never have had capacity, in which case the test is meaningless. However, the court recognized that substituted judgment could be a legitimate factor in deciding what is in best interests, and that has been incorporated into the MCA.

There are many cases on best interests, and most of them simply turn on their own facts. A recent case, *Re IH (Observance of Muslim Practice)* [2017] EWCOP 9, concerned a 39-year-old man suffering from a profound learning disability. Due to this impairment he had no understanding of religion and religious observations. The Court of Protection had to decide whether it was in his best interests, firstly, on the application of the Official Solicitor, to be required to fast during the daylight hours of Ramadan, and secondly, on the application of his father, to be required to have his axillary and pubic hair trimmed in accordance with Islamic culture and religious practice. The judge held that it was not in his best interests in both cases. In the case of fasting, the judge held that the man had no understanding of the religious significance of the withholding of food and water, and this would cause him distress and he might become distressed and/or aggressive. There was also concern that it might increase the side effects of his medication. In the case of the trimming of hair, again he would not understand why this was being done, and again it was likely to cause him distress and/or anger. The trimming of hair is part of the Islamic tradition of 'ritual cleanliness', but the judge held that he would derive no spiritual benefit from this, as he already had an elevated status because of his incapacity. The latter aspect is interesting in that it requires a view to be taken that without capacity, observance of religious practices is not required because of something akin to the absence of free will.

In *Cheshire & Wirral Partnership NHS Foundation Trust v Z* [2016] EWCOP 56, the case before the Court of Protection concerned a patient detained under section 3 of the MHA. We consider the MHA later in the chapter and although there is no reference to 'best interests' under the Act, this case effectively decided what was in the best interests of this patient without consideration of her capacity, because as she was detained under the Act she could be treated without consent even if she had capacity. She had suffered from a very extreme form of anorexia nervosa since the age of 15. Now aged 46, apart from her eating disorder and the underlying psychological problems, she was developing physical ill health, in particular severe osteoporosis. Her dangerously low weight was such that she was detained under section 3 of the MHA, not, of

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course, because of her physical condition, but because of her mental disorder and the fact that she posed a danger to herself. Her medical team had three options for treatment. The first was to continue to detain, and feed her under restraint. The second was to detain and feed her under sedation. The third was that she should be discharged from the section 3 detention and treated voluntarily. The evidence was that the first option posed a serious risk to her musculoskeletal integrity because of her osteoporosis, and the second option posed a similarly serious risk of her undergoing respiratory or cardiac arrest because of her overall physical fragility. The third option was held to be the best one for her, as the team had stressed that she could return to hospital at any time, and there was evidence that her mental state improved when not being subjected to enforced treatment. Even though she had a 30-year history of not cooperating with treatment regimes, the third option, it was held, would at least preserve her dignity and autonomy. The use of the last word is interesting as it could imply that she did have capacity.

It is worth pointing out that, just because the courts are considering *best interests* (emphasis added), it does not mean that the best possible course of action must be on offer. In (1) *ACCG* (2) *ACC v (1)MN (2) MR N (3)MRS N* [2017 UKSC 22], the UK Supreme Court stated that when the Court of Protection was making decisions on behalf of incapacitated adults, the court was limited to what the public authority (in this case, the appropriate Clinical Commissioning Group) would agree to implement, i.e. there could be no hypothetical proposals advanced as being in the best interests of the incapacitated person that a public authority would then be bound to implement.

The additional factor in best interests is that an act or decision must be arrived at after due consideration has been given to achieving the least restrictive effect on the person's rights and freedom of action. This leads us to consider the Deprivation of Liberty Safeguards.

Deprivation of liberty safeguards (DOLS)

The history of these safeguards goes back to the use of section 131 of the MHA 1983, which permits patients to enter psychiatric hospitals as informal patients, who in theory are free to leave at any time. In *R v Bournewood Community and Mental Health NHS Trust ex p L* (1998) 3 All ER 289, an autistic man had been admitted informally to a mental health unit. He normally lived with carers who understood him very well, but on this occasion at the day centre he visited he became very distressed, and it was felt appropriate to take him to the unit. When he arrived at the unit, he was described as being 'compliant' and he remained there for several months. The treating psychiatrist stated that if he had resisted treatment and confinement then they would have gone through the process of formal detention. The House of Lords was divided on the approach to this but decided that he was being treated under the common law doctrine of necessity, i.e. in his best interests. This doctrine had always been applied to emergency medical treatment, where patients

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are often treated without consent as they are unconscious or unable to give consent for other reasons. The common law had elaborated on this to justify treatment of incapable patients 'in their best interests' in non-emergency situations. In most circumstances this is sensible and uncontroversial, but in a few key areas, e.g. mental health, it is fraught with difficulty. There was a subsequent application to the European Court of Human Rights (*HL v United Kingdom* (2005) 40 EHRR 32). Under Article 5 of the European Convention on Human Rights, there is a right not to be deprived of liberty save in specific circumstances, and, in any event, there must be adequate safeguards to protect a person who is deprived of their liberty unlawfully. Not surprisingly, the Court found that there had been a violation of Article 5. This was because the deprivation was based entirely on the clinical assessments at the hospital and there was not an appropriate vehicle for the patient to use to obtain a speedy resolution to the situation, as informal patients are not subject to the Mental Health Review Tribunal process that applies to patients who are compulsorily detained. The other point in relation to this case and the European Convention is that the Convention only can only be invoked against actions that are attributable to the state. This is because if there is scope for private bodies to breach Convention Rights, then legal and regulatory regimes should be imposed by the state to prevent this happening.

As a result of this case, the government amended the MCA to include the Deprivation of Liberty Safeguards (DOLS) contained in sections 4A and 4B of the Act. They apply to anyone aged 18 or over, and cover patients in hospitals and people in care homes registered under the Care Standards Act 2000, whether private or publicly owned, but note later on, where we consider subsequent case law that suggests a wider ambit. If there is a person or a patient, the hospital or home must apply to the supervisory body (the local authority) for authorization of deprivation of liberty if it is believed that the person lacks capacity and has been deprived, or risks being deprived, of his liberty. Being deprived of liberty is not just being in a locked ward or care home; it can consist of treatment within the unit, such as confining people to chairs or similar restrictions. Deprivation of liberty can also be authorized by the Court of Protection. It will immediately be seen that there is much scope for avoidance of the authorization process in that this will depend upon the subjective assessments of whether someone is being deprived of his liberty (apart from undertaking the normal difficulties of assessment of capacity) and how far people running care homes, for example, are aware of precisely what deprivation of liberties may consist of. The DOLS are frequently criticized as being fundamentally flawed. Jones (2008) suggests that a '... procedure has been created that is hugely complex, voluminous, badly drafted, overly bureaucratic and difficult to understand, and yet provides mentally incapacitated people with minimum safeguards'.

The European Court of Human Rights has held that there are two elements of a confinement that must be satisfied in order for there to be a

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deprivation of liberty. First, there has to be established an objective element of confinement to a certain limited place for a not-negligible length of time, and second, there is the subjective element, which means that there has been no consent to the confinement (*Storck v Germany* (2005) 43 EHRR 96). A recent Court of Appeal decision, applying these criteria, while concerned with young women, is nevertheless applicable to the situation of many older people. *P and Q and Surrey County Council v CA and LA and Equality and Human Rights Commission* (2011) EWCA Civ 190, concerned two girls, described as having middle to severe learning difficulties, one of whom lived in a foster home and the other in a small specialist unit. The Court of Appeal held that there was no deprivation of liberty. The judge at first instance had held that, since they were happy in their care environments, there was no deprivation as this contentment was relevant to the objective element of confinement. The Court of Appeal rejected this as being relevant to this aspect, but stated that it was relevant to whether any deprivation was in their best interests. Lord Justice Wilson stated that persons living at home will not normally be deprived of their liberty, and a foster home or a carer's home was not much less 'normal', and 'even when the person lives in an institution rather than in a family home, there is a wide spectrum between the small children's home or nursing home, on the one hand, and a hospital designed for compulsory detentions like Bournewood; and it is in my view necessary to place each case along it' [para. 28]. This case was appealed to the Supreme Court where it was conjoined with another case which concerned an adult with cerebral palsy who lived in local authority accommodation with two other residents. He needed help with all the activities of daily living, but saw his mother regularly, went to a day centre, and participated in various social activities. The Court of Appeal went on to develop the concept of 'relative normality', stating that it was wrong to compare someone whose capacity was impaired with someone who was unimpaired, where control and supervision would be a deprivation of liberty.

In the UK Supreme Court (*Cheshire West and Chester Council v P and Surrey County Council v P* [2014] UKSC 19), the appeals were allowed. In *Cheshire West*, the life of P was completely controlled and therefore it amounted to a deprivation of liberty, and in *Surrey County Council*, it was held that the fact that people were happy and supported in their environment was not a factor when deciding deprivation of liberty because, as we have seen in the *HL* case, compliance has no effect upon whether there has been such a deprivation. The Supreme Court set down what Lady Hale referred to as the acid test. This is simply that when someone is under the complete control and supervision of those caring for them and are not free to leave the place where they live, they are deprived of their liberty. Lady Hale went on to say that: 'Furthermore, that deprivation is the responsibility of the state. Similar constraints would not necessarily amount to a deprivation of liberty for the purpose of article 5 if imposed by parents in the exercise of their ordinary parental responsibilities and outside the legal framework governing state

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intervention in the lives of children or people who lack the capacity to make their own decisions.’ [para. 54]. In a phrase that is frequently quoted she also stated that ‘a gilded cage is still a cage’ [para. 46].

This point was considered by the Court of Appeal in *Secretary of State for Justice v (1) Staffordshire County Council (2) SRK (by his Litigation Friend, SK) (3) RK (4) Irwin Mitchell Trust Corp* [2016] EWCA Civ 1317. As a result of receiving damages for personal injury, K received 24-hour care that was managed by the Irwin Mitchell Trust Corporation, which had been appointed by the Court of Protection to act as K’s representative (‘deputy’ in the language of the MCA; see ‘Procedural matters’). The deputy informed the local authority that, due to the accommodation arrangements, there may be a deprivation of liberty and a welfare order was applied for, and granted by the Court of Protection as, although these were private care arrangements, there were insufficient procedural safeguards to satisfy the state’s positive obligations under Article 5. The Secretary of State appealed on the basis that the criminal and civil law, and enforceable obligations on public bodies in respect of vulnerable people were sufficient to satisfy this. The Court of Appeal dismissed the appeal on the basis that the operation of the law relied upon by the Secretary of State, was dependent upon wrong-doing being brought to the attention of the state; there was no process of assessment and review of such private care to provide the necessary safeguards.

In 2014, via the process of post-legislative scrutiny, the House of Lords Select Committee made a number of recommendations as to the operation of the MCA. One was that there be an independent body to oversee the functioning of the MCA (<https://publications.parliament.uk/pa/ld201314/ldselect/ldmentalcap/139/139.pdf> Recommendation 4, para. 14) and the other key finding expressed concerns about the DOLS. The view was that the safeguards do not provide sufficient protection, and that the legislative provisions should be re-drafted (<https://publications.parliament.uk/pa/ld201314/ldselect/ldmentalcap/139/139.pdf> Recommendation 14, para. 34). In addition, it was clear that *Cheshire West* would significantly increase the number of DOLS. This, plus the Select Committee Report, resulted in the Law Commission undertaking consultation on the operation of the Act. The Commission reported in March 2017, making a number of recommendations. In the context of DOLS, it recommend that there should be increased rights to instruct an independent advocate (at the moment under the MCA there is provision for the independent advocates to be available in certain circumstances); a system of inspection and review of the circumstances in which people are deprived of their liberty; the extension of the powers to authorize a deprivation of liberty; extending DOLS to those aged 16 and 17; a simplified version of the best interests assessment which emphasizes that, in all cases, arrangements must be necessary and proportionate before they can be authorized. There was also some rather vague reference to human rights, and the fact that protection should be

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extended to all care settings, including domestic settings, on the basis that this would avoid applications to the Court of Protection.

The government eventually responded by passing the Mental Capacity (Amendment) Act 2019, which replaces DOLS with new measures known as Liberty Protection Safeguards, intended for introduction in 2020. These are intended to be simpler to operate, but much will depend on the content of the accompanying Code of Practice, which is still being developed.

Advance decisions and lasting powers of attorney

First of all, these should properly be described as advance 'refusals' in that no patient, whatever the treatment concerned relates to, can make an advance request for a specific treatment, or, at least, he could make a request, but no clinician would be bound by it. The law therefore permits people only to say what treatment they do *not* want in the event of them losing their capacity. Sections 24–26 of the MCA effectively codify the previous common law position, where advance decisions were recognized. In order to make an advance decision, one has to have capacity and be aged 18 or over. The decision will bind treating physicians if the patient loses capacity. However, the sticky points are contained within section 25, which states that the decision must be both 'valid' and 'applicable'. The decision must not have been withdrawn by the patient, but also must not be inconsistent with subsequent behaviour of the patient. The Explanatory Notes to the MCA give the example of a patient who was formerly a Jehovah's Witness who made an advance decision of refusal of blood transfusions and who later married into the Muslim faith, but has forgotten to destroy the advance decision. It will also only be valid if the patient has lost capacity; one would hope this would be self-evident, but it is correct to make this beyond doubt. The circumstances in which the decision, while valid, might not be applicable are those where the decision is not clear as to the circumstances in which it would apply, or that new treatments have become available for conditions when there were no treatments, or much less onerous treatments are now available. Section 25(5)–(6) contains a number of additional formalities that have to be complied with if the refusal is of life-sustaining treatment. An advance decision will not be valid if, subsequent to it, the patient gives another person a Lasting Power of Attorney under section 9. These cover personal care and treatment, whereas the 'Enduring Powers of Attorney' that preceded the MCA had a much more restricted remit.

Procedural matters

It is outside the scope of this chapter to examine the detail, but it is worth pointing out that most decisions on behalf of incapacitated patients will be made by relatives, carers, social workers, and healthcare professionals, without any reference to the courts. However, there is provision within the MCA of new powers for the Court of Protection; prior to the MCA, this court only dealt with the property affairs of incapable

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people, but these powers have been extended to include all personal welfare decisions. The court is mostly populated by judges from the Family Division of the High Court. The court can make declarations as to whether someone has capacity to make particular decisions, or whether a course of action is in his best interests, or whether a valid advance decision exists and whether it is applicable; deal with financial matters, e.g. authorizing the sale of property; resolve issues relating to lasting powers of attorney; and appoint deputies to make decisions for incapable people for whom less formal processes are not available. The MCA does also provide for Independent Mental Capacity Advocates to be appointed in cases where the person has no one else who can be consulted on best interests.

Finally, it has been held that the MCA has not ousted the High Court's inherent jurisdiction to deal with cases that fall outside the Act, and to protect vulnerable adults who were under constraint, subject to coercion or undue influence, or deprived of capacity for some other reason (*DL v A Local Authority and Others* (2012) EWCA Civ 253).

Adults with Incapacity (Scotland) Act 2000

The MCA only applies in England and Wales. The Scottish Act is somewhat different from the MCA in that it does not use the concept of best interests in decision-making, rather referring to whether any act done in connection with the incapacitated adult is for his 'benefit' (section (1)(2)). The reasoning behind this is that the notion of best interests is more paternalistic as it was developed in the context of the law relating to children, and the concept of benefit is more respectful of the individual's own wishes. Arguably, it is a question of semantics, because under the MCA (section 4(6)) there is a requirement that, in deciding what is in the best interests of the patient, the past and present wishes, feelings, beliefs, and values of the patient must all be taken into account.

The Mental Health Act 1983 (MHA)

Given that a significant number of older people who come within the ambit of psychiatric services will be living with dementia or related mental disabilities, the Mental Capacity Act 2005 will almost certainly be the most commonly used legislation. However, there can be circumstances in which it may be more appropriate to use the mental health legislation that provides for compulsory detention of patients. Although the MHA does provide for detention of people who have come through the criminal justice system and for whom it is more appropriate to receive treatment rather than mere custody, it is outside the scope of this chapter, which is concerned with civil admissions only.

There was a move in the late 1990s to reform the MHA of 1983, and in 1998 the government set up a scoping study review committee to report. The report ('Richardson Report') focused upon patient-centred reform, but the recommendations were not followed. In addition, because of

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concern about dangerous patients not being compulsorily detainable, the Home Office issued a consultation document on Managing Dangerous People with Severe Personality Disorder (DPSD) that put forward draconian proposals. The principal impetus for this was the case of Michael Stone, who committed homicide following release from a psychiatric hospital, on the basis that he suffered from a psychopathic disorder and the Act provided that such patients could not be detained for long-term treatment if they were deemed to be 'untreatable' (for an appraisal of DPSD and its limited clinical utility, see Duggan, 2011). Again, this initiative gathered dust, as did a number of other attempts to make changes to the 1983 Act. Finally, the MHA 2007 made a relatively modest number of changes to the 1983 Act. It is important to remember that the 2007 was an amending Act and the 1983 is still the current Act in force.

The main provisions of the Act remain the same. The power to compulsorily detain for both short and long term remains and the criteria to be satisfied are the same: basically, the patient has to be suffering from some form of mental disorder and he has to be a danger to himself or to others. These requirements are fairly standard in the legislation in other jurisdictions, too. There are four main changes. First, the Act provides for an independent advocacy scheme for those patients who have been detained but have no other form of representation. Second, where it is considered necessary to detain patients for longer than 28 days, the requirement that they be suffering from conditions such as 'mental illness', 'mental impairment', and 'psychopathic disorder' has gone (the last condition no doubt having bemused clinicians for some time). For any form of detention, the patient just has to be suffering from 'mental disorder'. Third, as an adjunct to this, the 'treatability' requirement has been removed. Under the original 1983 Act, for long-term detention the patient had to be suffering from mental illness, mental impairment, severe mental impairment, or psychopathic disorder and, in the case of non-severe mental impairment and psychopathic disorder, the patient had to be 'treatable'. Part of the definitions of non-severe mental impairment and psychopathic disorder was that they both be associated with 'abnormally aggressive or seriously irresponsible conduct on the part of the person concerned'. The requirement that these patients be treatable was based upon the Percy Commission's recommendations, upon which the 1959 MHA was based, and the requirement was re-enacted in the 1983 Act. Commendably, these recommendations sought to preserve civil liberties and protect citizens from detention before they had committed a criminal act: 'If one is to apply preventive control to psychopathic patients under wider conditions than these, one is in effect applying to them preventive detention in hospital in circumstances which would not justify preventive detention in prison under the criminal law' (Percy Commission, 1957).

Unfortunately, laudable as these sentiments were, the consequences were not always good. Some such patients can be extremely difficult to manage

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and the treatability condition meant that a decision to discharge them could be exercised on this basis. Of course, as far as older people are concerned, while they may well have fitted into this category because of 'irresponsible conduct', they would be easier to manage because they would often be more physically frail. The fourth major change to the Act has been the introduction of compulsory treatment in the community, which is an attempt to deal with the well-known 'revolving door' syndrome, i.e. certain patients, such as those suffering from psychosis, would be compulsorily admitted to hospital, stabilized, and discharged, only to neglect to take medication and find themselves back in hospital.

The basis of civil detention under the MHA is roughly the same as in many other jurisdictions, i.e. in addition to being mentally disordered the patient must pose a risk to himself or to others. It is beyond the scope of this chapter to debate the libertarian issues at the heart of this, but suffice it to say that there are two key issues here. First, some would argue that, although it is understandable that society wants to do something about those who pose a risk to others, apart from those with mental health problems, we wait for people to commit criminal offences before any action is taken against them; and second, if we can justify detention because of the threat to others, why should people, who merely pose a risk to themselves, be detained?

Informal admission

As discussed earlier, a misuse of section 131 of the MHA led to considerable litigation and an eventual visit to the European Court of Human Rights. The Act continues to provide for informal admission under section 131. It was originally part of the legislation for the avoidance of any doubt that statutory provisions that provide for compulsory admission for psychiatric patients do not imply that patients who are admitted for inpatient psychiatric treatment have to be admitted via the use of compulsory measures. Such patients are described as 'informal' patients, because to call them 'voluntary patients' suggests that they have capacity, and, as has been shown, section 131 can be used for 'compliant' patients lacking in capacity and they are protected by the DOLS. Informal patients are free to leave hospital at any time and cannot be treated without their consent.

Compulsory detention under the Act—the key players

The approved mental health professional (AMHP)

This is the new title for the professional formerly called the 'approved social worker'. The role is the same in that the AMHPs have, under section 13 of the Act, a duty (note that a duty is more than a power) to make an application for admission to hospital or an application for guardianship if they are satisfied that an application should be made. They are required to have regard to any wishes expressed by relatives or the patient and any other relevant circumstances. It should be noted that

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this is a *personal* duty and not a duty as a functionary of the local authority that has appointed them.

The nearest relative

A nearest relative (defined under section 26 in descending order of proximity of relationship) can also apply for the patient to be admitted under the Act. There was an earlier proposal in the debate about reform of the MHA to abolish and/or change the role of the nearest relative. However, it has remained with a small but significant change in that the patient can apply to the court under section 29(3) of the MHA for his nearest relative to be displaced on the ground that he is unsuitable to act. Although the nearest relative is defined under section 26, under the displacement provisions of section 29(3), anyone who is suitable can be appointed as the patient's nearest relative.

The doctors

The application for detention must be supported by medical recommendations, and normally this will be two recommendations. However, in emergencies (see Admission for assessment in emergencies—section 4), one recommendation will suffice.

Compulsory detention under the Act—the criteria

The requirement that patients be suffering from mental disorder

Patients cannot be detained unless they are suffering from mental disorder, and the definition of mental disorder (section 1(2)) is exactly the same as the definition in the Mental Capacity Act 2005, i.e. any disorder or disability of mind, which, pursuant to section 1(3), does not include addiction to alcohol or drugs, although 'dual diagnosis' is possible. That is, people who have a mental disorder and an addiction can be detained under the MHA as it was recognized that there was a risk of patients being denied help by both the mental health services and those dealing with substance misuse. For further information interested readers are referred to the Department of Health guidance.

People living with a learning disability shall not be considered to be suffering from mental disorder unless the disability is associated with abnormally aggressive or seriously irresponsible conduct. It was held in *Re F (Mental Health Act: Guardianship)* (2000) 1 FLR 192 that 'seriously irresponsible' has to be linked to a significant risk of harm to self or others, so a 17-year-old who wanted to go home, where she had been severely neglected, was not being seriously irresponsible.

It should also be noted that if the patient is subsequently found not to have been suffering from mental disorder at all, there will be no illegality in the detention (*R v Kirklees Metropolitan BC ex p C* (1993) 2 FLR 187).

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Admission for assessment—section 2

Although the section refers to assessment, quite rightly, treatment can be given to the patient under section 2 detention, but the primary purpose is to provide for a short-term admission to decide what might be needed in the long term. The patient must be suffering from mental disorder 'of a nature or degree which warrants the detention of the patient *in hospital*' (emphasis added) and he 'ought to be so detained in the interests of his own health or safety or with a view to the protection of other persons'. For section 2 applications made by an AMHP, there is no requirement that the nearest relative be consulted, but that person should be informed that an application is to be made, and if the nearest relative expresses any wishes, then these should be taken into account by the AMHP (section 13(1)).

Admission under this section is for a maximum of 28 days and is not renewable, but it has been held that the discretion to make an application should not be fettered in any way (*R v South Western Hospital Managers ex p M* (1994) 1 All ER 161). Thus, a second section 2 application made immediately after the expiry of the first one might be justifiable, although it would certainly be open to an application for judicial review.

Admission for treatment—section 3

If further detention after a section 2 admission is required, then normally this would be made under section 3, where the conditions are that it has to be 'necessary' for the patient's health and safety or for the protection of others, and that it is appropriate for him to receive treatment in hospital and this cannot be provided unless he is detained. It may be a matter of semantics, but the difference in the wording means that 'ought to be detained' under section 2 is not as stringent as it being necessary, which implies that there is a bigger threat to health and safety in the case of a section 3 admission. Admission under section 3 is for six months and is renewable.

Admission for assessment in emergencies—section 4

If there is an 'urgent necessity', then an application can be made under section 4 which requires only one medical recommendation. The wording of the section should be heeded and this power should not be used in cases where it is simply more convenient to admit in this way; it is there to apply to genuine emergencies only. The admission only lasts for 72 hours, so that a second recommendation should be obtained before the expiration of that period.

Admission for inpatients—section 5

In the case of an informal patient, he may decide to discharge himself from hospital. Similar provisions as section 4 apply in such a case and the

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admission lasts for 72 hours. Suitably qualified nurses also have a similar holding power in such cases, which lasts for six hours.

Leave of absence

Under section 17 of the MHA, the responsible clinician has the power to grant a leave of absence to a patient detained under section 3. The court has been reluctant to distinguish between in-patient and outpatient treatment, so that it has rejected a judicial review claim from a patient detained under section 3, and where an application was made for a renewal of her detention where her treatment plan consisted entirely of treatment within the community (*R (On the Application of DR) v Mersey Care NHS Trust* (2002) All ER(d) 28). The purpose of it was originally to permit treatment in the community, so it is questionable whether section 17 would be used in such cases, given that it is now possible to make community treatment orders. Certainly, judicial review should be successful if section 17 was now used for this purpose.

Guardianship—section 7

This is a little-used power. It is not about detention of a patient, nor is it about medical treatment. It is about general personal care. The requirement, in addition to suffering from mental disorder (which in the case of someone with a learning disability has to be coupled with abnormally aggressive or seriously irresponsible conduct), is that the mental disorder warrants reception into guardianship. Normally the guardian will be the local authority, but that is not a condition under the MHA. The powers of the guardian are to require specified residence, to require attendance for medical treatment, education, and training, and to require access to the person concerned. There can be no insistence on any form of treatment. It might be appropriate to use this in the case of an older person with or without capacity if he is neglectful of his personal needs and there is no better way to manage it, but, as we have seen, much can be done under the MCA in the best interests of the person concerned.

Treatment of those who are compulsorily detained

Section 63—treatment where no consent required

This does not apply to those detained under sections 4 and 5 and does not apply to guardianship. It states that consent is not necessary for treatment to be given to patients if it is treatment for the mental disorder. 'Mental disorder' has been given a very wide interpretation by the courts because it is defined under the MHA as including 'nursing, and also includes care, habilitation, and rehabilitation under medical supervision' (section 145(1)). It has included force-feeding for a patient classified as being psychopathic who was refusing to eat as a form of self-harm (*B v Croydon Health Authority* (1994) 2WLR 294), but it was held by the Court of Appeal in *St George's Healthcare NHS Trust v S* (1998) 3 All ER 673 that it has to be treatment for a condition that is integral to the

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mental disorder, which perhaps does not take us a great deal further forward.

The relationship between section 63 and advance decisions under the MCA was considered in the case of *Nottinghamshire Healthcare NHS Trust v RC* [2014] EWHC 1317 (COP). This concerned a man with a serious personality disorder who was detained under the MHA. Being a Jehovah's Witness, he had made an advance decision to refuse blood products. He self-harmed and the question arose as to whether he could be given blood products as he was on anticoagulants due to a history of thrombosis. The advance decision was not relevant as this would only be had regard to, if, and when, he lost capacity. The decision to be made by the court was whether he could still be given blood products under the provisions of section 63. It was held that to allow this would be an abuse of power and would be a denial of a most basic freedom.

Sections 57, 58, and 58A

These are treatments to which section 63 does not apply. As consent is necessary, these treatments cannot be given to anyone who lacks capacity. Section 57 requires the consent of the patient *and* a second opinion and is about the most controversial treatments. It covers psychosurgery and any other form of treatment specified by the Secretary of State (at present the only specified treatment is surgical implantation of hormones to reduce the male sex drive).

Section 58 and 58A treatments require consent *or* a second opinion. Section 58 treatment is the administration of medication in excess of a period of three months. Section 58A treatment is electroconvulsive therapy or any other treatment specified by regulations made by the 'appropriate national authority'.

Section 62—urgent treatment

Despite needing consent, this part of the MHA provides for the requirements of sections 57 and 58 to be dispensed if urgent treatment is necessary. The treatment must either i) be immediately necessary to save the patient's life; ii), being irreversible, be immediately necessary to prevent a serious deterioration of his condition; iii) not being irreversible or hazardous, be immediately necessary to alleviate serious suffering by the patient; or iv) represent the minimum interference necessary to prevent the patient from behaving violently or being a danger to himself or to others. Where the treatment is under section 58A, then the treatment has to be necessary under scenarios i) or ii). Section 57 treatments would be unlikely to satisfy the condition section in terms of hazard/irreversibility. The circumstances in which section 62 would apply therefore are most likely to be in relation to section 58 in a case where the three-month period for the administration of medication was about to elapse and it was not possible to obtain a second opinion in time.

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Community treatment orders (CTOs)

Introduced into the MHA by the MHA 2007, CTOs (section 17A) can only be made in respect of patients who have been discharged from hospital having been detained under section 3. In a case where a CTO was thought desirable for a section 2 patient, therefore, it would be necessary to detain under section 3 and then discharge the patient. An AMHP and the responsible clinician have to be satisfied that the patient is suffering from a mental disorder of a nature or to a degree that makes it appropriate for him to receive medical treatment and that it is necessary for the patient's health or safety, or for the protection of others, that the patient should receive treatment, and that it can be provided in the community. The last condition is subject to the power to recall the patient to hospital and it must be necessary for this power to be applied. The patient does not have to consent, but it is unlikely that a CTO would be made if the patient objected.

Looking back to the DOLS, the case of *PJ (A Patient) v Local Health Board* [2015] UKUT 480 (AAC) examined the question as to whether the conditions of a CTO would result in an unlawful deprivation of liberty. In PJ's case, he was discharged to a care home, would be subject to the regime of that home, and if allowed leave in the community he would be subject to provisions for revocation of that leave and the triggering of absconding protocols. The Mental Health Review Tribunal had held that that there was no deprivation of liberty as there was no continuous control and supervision, and that the CTO took precedence over human rights issues. The Upper Tribunal allowed the appeal on the basis that the granting of a freedom to 'take leave' that could be revoked, constituted a deprivation of liberty. It stated that Tribunals should address the following questions: would the conditions, on an objective assessment, result in a deprivation of liberty; if so, had the patient the capacity to consent to this; would this consent avoid a breach of Article 5; if the patient lacked capacity could the deprivation be authorized under the MCA; whether section 64D of the MHA (the provision that provides that patients lacking capacity can be given treatment in the community) can be relied upon to avoid a breach of Article 5, and how the aforementioned matters should be taken into account by a tribunal in deciding whether to uphold a CTO or discharge it.

Leaving hospital

First, it must be noted that the patient can be discharged under section 23, although it is lawful to delay discharge, even if there is no longer a justification for detention, if there is good reason to do so, e.g. putting into place aftercare facilities under section 117.

Second, detention can be challenged in one of three ways. Under section 66, patients have a right to apply to a Mental Health Review Tribunal for a review of their case. The nearest relative also has a right to apply, and there is an automatic review process under section 68, whereby hospital

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managers must refer to a Tribunal any patient admitted for treatment who has not exercised his right to apply within the first six months. The remit of the Tribunal is to decide whether the conditions for detention under the MHA still apply. However, there may be irregularities that cannot be remedied by use of the statutory review system, and in those circumstances the common law remedies of habeas corpus and judicial review may be used. For example, any allegation that there is a breach of the Human Rights Act 1998 would be made via judicial review.

Finally, it should be noted that although the Care Quality Commission cannot act to remove patients from detention under the Act, it does hear complaints and its members make hospital visits.

Relationship between the Mental Health Act 1983 and the Mental Capacity Act 2005

As demonstrated, there are two quite separate regimes at play in this area. The MCA is primarily about treatment in best interests and about using the least restrictive treatment of patients where possible. It is about taking into account the beliefs and wishes and feelings of the patient when deciding on the best course of action. The MHA is partly about protecting the patient from self-harm, but is also about protecting the public and doing this via a system of restraint and compulsory treatment.

There could be a great deal of temptation for treating clinicians in a formal MHA situation to state that it is in the patient's best interests to be detained. However, if the formal detention provisions of the MHA apply, then the MCA has no part to play, even if the patient lacks capacity. Paragraph 5 of Schedule 1 of the MCA states that:

2. P is ineligible [to be deprived of his liberty] if the following conditions are met.
3. The first condition is that the relevant instrument authorises P to be a mental health patient.
4. The second condition is that P objects—
 - (a) to being a mental health patient, or
 - (b) to being given some or all of the mental health treatment.

It was confirmed in the case of *W Primary Care Trust v TB* (2009) EWHC 1737 that this means that if the patient objects to confinement and the admission criteria under the MHA are met, then the MCA should not be used. Schedule 1A of the MCA lists a number of factors that should be taken into account in deciding whether the patient 'objects', including behaviour, wishes, feelings, views, beliefs, and values. However, as Richardson (2010) points out: 'provided these statutory factors are *taken into account*, clinicians are free to use their own judgment in determining the presence or absence of objection. This may present clinicians with welcome discretion when dealing with individual cases, but it provides little certainty for those directly affected by the eventual decision'.

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It is only when patients are informally admitted for treatment for mental disorder that the DOLS apply, and in all other respects, such as the applicability of the MCA principles or the requirement of best interests, the MCA applies. In making psychiatric treatment decisions, therefore, the key considerations are whether the provisions of the MHA are satisfied and whether there is any objection on the part of the patient. However, if we look back to best interests, and the case of *Cheshire & Wirral Partnership NHS Foundation Trust v Z* [2016] EWCOP 56, we can see that, out of the treatment options available to a patient who clearly could be detained under the MHA, what was 'best for her' was the basis for deciding whether the section 3 detention should be discharged.

The relationship between the two pieces of legislation was considered in the case of *J v Foundation Trust* (2009) EWHC 2972 Fam, which concerned a 65-year-old man who suffered from vascular dementia and Korsakoff's syndrome. He also suffered from diabetes but because of his mental disorder he was unable to manage his diabetes appropriately, running the risk of death or serious injury. He was detained under section 2 of the MHA for assessment, but later treated under the MCA, by way of a standard authorization for deprivation of his liberty, initially at a clinic and later in a care home. He objected to being detained insofar as his detention was for treatment of his mental disorder. The judge held that J was receiving treatment in hospital to make sure he took medication for his diabetes, and not to ensure treatment for mental disorder, and that he was only given medication for his mental disorder if he did not object to taking it. Consequently, if the need for physical treatment had not existed, J should not have been detained in hospital to receive his mental treatment, and so the only effective reason for his detention was his need for physical treatment. The DOLS authorization therefore did not authorize J to be a mental health patient. The same approach resulted in the conclusion that J was not within the scope of the 1983 Act, and J's objections to treatment for mental disorder were of academic interest only.

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