DRUGS

DRUGS IN NEUROLOGY

Edited by Sathiji Nageshwaran | David Ledingham
Heather C. Wilson

Covers the breadth of medications used in modern neurology with a clinical focus

Practical aspects related to prescribing and therapeutic drug monitoring are covered

Based on the most up-to-date evidence-based guidance

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Drugs in Neurology

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Edited by

Sathiji Nageshwaran

Wellcome Trust Translational Medicine and Therapeutics Fellow, Imperial College London, UK; Honorary Clinical Fellow in Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

David Ledingham

Neurology Registrar, Department of Neurology, Royal Victoria Infirmary, Newcastle Upon Tyne, UK

Heather C Wilson

Consultant Neurologist and Honorary Clinical Lecturer, Royal Free London NHS Trust, UK; Honorary Consultant Neurologist, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

Associate Editor

Anthony Dickenson

Professor of Neuropharmacology, Neuroscience, Physiology, and Pharmacology, University College London, UK

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Foreword by Professor Matthews

The amount of information that neurologists need for safe and effective practice has grown rapidly over the last generation as neurology has moved from a focus on diagnosis to one on treatment. As a consequence of this, the busy general neurologist or trainee faces new challenges in managing pharmacological treatments. This practical handbook, with its succinct summaries of widely accepted management approaches to diseases commonly encountered, and well-set out, detailed information on individual drugs, goes a long way towards addressing this challenge. It will be a welcome addition to my clinic desk.

Nageshwaran, Ledingham and Wilson have brought a range of experience to developing a text that will help doctors with very different levels of expertise. For those in training or approaching an area with which they are less familiar, the short chapters describing common syndromes and their management provides a quick review. While a sub-specialist might quibble with details, the approaches are sensible and reflect mainstream British practice. Particularly welcome are the well-selected references to the evidence base for treatments. These include the key points needed to explain to patients why they are being treated to engage them as a first step towards enabling them to be a full partners in their disease management.

For more experienced neurologists, the tables comparing pharmacological characteristics and the associated reminders of drug monitoring requirements and interactions provide important, practical aids to better practice. I find the pharmacokinetic data especially useful. Like all of the other data pulled together here, while available elsewhere, it can be difficult to access quickly when it is needed. The range of data summarised has been chosen thoughtfully. The tables also are set out well and in a typeface that doesn't challenge the aging neurologist's eyesight!

The role of reference books in an age of apps is increasingly questioned. This volume illustrates why there is still a place for the book. It is well edited, providing information selected to address practical clinical problems by a group of authors aware of the needs of both trainees and experienced clinicians who have "seen it all". As another volume in a respected series, the reader can have confidence in the quality of the data. Finally, it is organised to suit needs of everyday practice, even to the extent that the early chapters are arranged in approximate order of the frequency with which the problems arise in usual clinic practice.

The authors are to be congratulated!

Paul M. Matthews, OBE, MD,
D Phil, FRCP, FMedSci
Imperial College London, 2016

Foreword by Professor Bronstein

There are several roles practicing clinicians play in caring for patients but none are more essential than providing an accurate diagnosis and prescribing the appropriate treatments. Neurological disorders have often been seen as some of the most challenging especially to the general practitioner and non-neurologist. Furthermore, there has been an explosion in our understanding of neurological disease over the past few decades making the task of providing high-level care even more daunting. Clinical-pathological phenotypes have been much better refined with the development of advanced imaging techniques and genetics. The sub-specialization of neurology has also grown in recent years with this improved understanding of the pathophysiology of common and rare neurological disorders. With these advances came new medications and repurposing of older medications. The sheer volume of information that a clinician must assimilate has become overwhelming.

How we find medical information has also changed over the past few decades. When I worked in Nicaragua 25 years ago, there were essentially no resources covering neurological disease and treatment beyond what I could carry. Conversely, while studying at the National Hospital in London, the library was overflowing with reference books and journals. Reviewing and filtering the massive amount of information was exciting but time consuming and not very practical for a practicing clinician. The Internet has provided an even larger array of information on neurological disorders and treatments but it also comes with important cautions. The accuracy and reliability of Internet sources always has to be considered and is not always clear despite thorough investigation.

Drugs in Neurology is a wonderful practical resource to help manage the massive amount of critical information needed to be an effective practicing clinician. The book is divided into two sections. The first section provides an up to date but succinct description of clinical conditions and approaches to management. There is a clear emphasis on evidence-based medicine. The second section of this book contains comprehensive specific information on classes of medications and specific drugs which are organized alphabetically. Included are details on mechanism of actions, pharmacokinetics and interactions, toxicity and side effects, contraindications, and evidence of efficacy. Tables are effectively used for drug comparisons and pertinent references are provided.

This book will find a place in my doctor's bag and will be helpful for any clinician treating patients with neurological conditions. This succinct, well-organized Internet-independent resource will find plenty of use both in the outpatient clinic and during inpatient hospital rounds.

Jeff Bronstein MD, PhD
David Geffen School of Medicine at UCLA
Los Angeles, 2016

Preface

A new era in clinical neurology is under way. In recent years, neurology has seen a shift in practice; many hitherto incurable neurological conditions can now be effectively treated. Thanks to new insights into pathophysiology, improved diagnostic tools, and a focus on translational research increasingly efficacious treatments are emerging.

With the rapidly evolving pharmacopeia used in modern neurology, there is now a need for a practical guide which provides an evidence-based approach enabling the user to choose the most appropriate therapy for the increasingly wide range of neurological conditions amenable to treatment.

Drugs in Neurology comprehensively covers the modern management of neurological diseases in adults. Emphasis is placed on the pharmacological underpinnings behind the drugs used and on the evidence base for their use, but respect is also given to treatment recommendations established as a result of decades of clinical experience and to opinions from experts in the field.

We hope this book will be of value to trainees in neurology and clinical pharmacology and to all those involved in the treatment of adults with neurological disorders.

We welcome comments and feedback from readers to help refine subsequent print and online editions of *Drugs in Neurology*.

Please e-mail all correspondence to: editors.drugsinneurology@gmail.com.

Dedication

This work is dedicated to all the patients we serve, who keep us inspired, motivated, and interested in their lives.

SN, DL, HW

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This work would not have been possible without the understanding and support of our families.

SN would like to thank his incredible mentors in clinical neuroscience that have supported him throughout his career: Dr Heather Wilson, Miss Joan Grieve, Dr Yvette Bordelon, and Professor Susan Perlman.

DL would like to thank his (equally incredible) mentors, past and present and the book's contributors, whose hard work forms the core of this book and who tolerated numerous queries and revisions (for the most part in good humour).

HW would like to thank all her colleagues and friends in the Neurology Department at the Royal Free Hospital who have inspired and supported her throughout her career. And in memory of George Harwood who will always be her greatest role model.

We would like to extend our sincere gratitude to OUP for their patience and guidance during the production of this book, in particular our commissioning editors Peter Stevenson and Lauren Dunn. It has been a long road, but we got there!

Contents

Contributors

Omar Abdel-Mannan
Academic Clinical Fellow,
Institute of Child Health,
London, UK

Peter Arthur-Farraj
Neurology Registrar,
Norfolk and Norwich University Hospital, Norwich, UK

Bal Athwal
Consultant Neurologist and Honorary Senior Lecturer,
Royal Free Hospital, Barnet Hospital, and University College Hospital, London, UK

Aravindhan Baheerathan
Core Medical Trainee,
National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

Arjun Chandna
Core Medical Trainee
Imperial College Healthcare NHS Trust, London, UK

Christopher P Conlon
Professor of Infectious Diseases and Deputy Head of Department,
Nuffield Department of Medicine, University of Oxford, Oxford, UK

Gerard Davies
Consultant Neurologist,
Royal Free Hospital, London, UK

Anthony Dickenson
Professor of Neuropharmacology,
Neuroscience, Physiology, and Pharmacology,
University College London, London, UK

Ayesha Ejaz
Core Medical Trainee,
University College London Hospital, London, UK

Sofia Eriksson
Consultant Neurologist and Honorary Senior Lecturer,
Department of Clinical and Experimental Epilepsy, National Hospital for Neurology and Neurosurgery, London, UK

Peter Garrard
Reader in Neurology,
Neuroscience Research Centre,
St George's, University of London, London, UK

Diego Kaski
Neurology Registrar,
Department of Neurology,
National Hospital for Neurology and Neurosurgery, Queen Square, London, UK;
Honorary Clinical Research Fellow, Department of Neuro-otology, Imperial College London, Charing Cross Hospital, London, UK

Meher Lad
NIHR Academic Clinical Fellow in Neurology, Newcastle upon Tyne Hospitals Foundation NHS Trust, Newcastle upon Tyne, UK

David Ledingham
Neurology Registrar, Department of Neurology, Royal Victoria Infirmary, Newcastle Upon Tyne, UK

Sathiji Nageshwaran
Wellcome Trust Translational Medicine and Therapeutics Fellow, Imperial College London, UK; Honorary Clinical Fellow in Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

Jalesh N Panicker
Consultant Neurologist in Uro-neurology and Honorary Senior Lecturer, The National Hospital for Neurology and Neurosurgery and UCL Institute of Neurology, Queen Square, London, UK

Philip N. Patsalos
Professor of Clinical Pharmacology, UCL Institute of Neurology, Queen Square, London, UK; Epilepsy Society, Chalfont Centre for Epilepsy, Buckinghamshire, UK

Susan Perlman
Professor of Neurology, David Geffen School of Medicine, University of California, Los Angeles, USA

Menelaos Pipis
Specialist Registrar in Neurology, Kings College Hospital, London, UK

Christos Proukakis
Senior Lecturer, UCL Institute of Neurology, Clinical Neuroscience, London, UK; Honorary Consultant Neurologist, Royal Free London NHS Trust, London, UK

Jeremy Rees
Consultant Neurologist, National Hospital for Neurology and Neurosurgery, University College London Hospitals Foundation Trust, London, UK; Honorary Senior Lecturer, UCL Institute of Neurology, London, UK

Samuel Shribman
Registrar in Neurology, St George's Hospital, London, UK

Sebastian M Toescu
Victor Horsley Department of Neurosurgery, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

Chris Turner
Consultant Neurologist and Honorary Senior Lecturer, MRC Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

Sam Walker
Specialty Registrar,
West Midlands Postgraduate School of Radiology,
Birmingham, UK

David Werring
Professor of Clinical Neurology,
Honorary Consultant Neurologist,
National Hospital for Neurology and Neurosurgery, Queen Square, University College Hospitals NHS Foundation Trust,
UCL Stroke Research Centre,
UCL Institute of Neurology,
London, UK

Heather C Wilson
Consultant Neurologist,
Royal Free Hospital, London, UK

Philip Xiu
GP registrar,
St James University Hospital,
Leeds, UK

Symbols and abbreviations

℘	website
~	approximately
°	degree
=	equal to
>	greater than
<	less than
≥	equal to or greater than
≤	equal to or less than
±	plus or minus
α	alpha
β	beta
δ	delta
γ	gamma
κ	kappa
μ	mu
%	per cent
£	pound sterling
®	registered trademark
4-AP	4-aminopyridine
A&E	accident and emergency
AAN	American Academy of Neurology
AbESSTT	Abciximab in Emergency Treatment of Stroke Trial
ABN	Association of British Neurologists
ACE	angiotensin-converting enzyme
AChEI	anticholinesterase inhibitor
AChR	acetylcholine receptor
AD	autosomal dominant; Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale cognitive subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study Activities of Daily Living
ADEM	acute disseminated encephalomyelitis
ADH	antidiuretic hormone
ADHD	attention-deficit/hyperactivity disorder
ADP	adenosine diphosphate
AED	antiepileptic drugs
AF	atrial fibrillation

AHS	American Headache Society
AIDP	acute inflammatory demyelinating polyradiculopathy
AIDS	acquired immune deficiency syndrome
AIP	acute intermittent porphyria
ALA	aminolevulinic acid
ALD	adrenoleukodystrophy
ALP	alkaline phosphatase
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
a.m.	*ante meridiem* (before noon)
AMAN	acute motor axonal neuropathy
AMN	adrenomyeloneuropathy
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMSAN	acute motor and sensory axonal neuropathy
ANA	antinuclear antibody
ANCA	anti-neutrophil cytoplasmic antibody
APLS	antiphospholipid syndrome
aPTT	activated partial thromboplastin time
AQP4	aquaporin 4
AR	autosomal recessive
ARB	angiotensin receptor blocker
ARR	annualized relapse rate
ASA	acetylsalicylic acid
ATACH	Antihypertensive Treatment of Acute Cerebral Hemorrhage
AV	atrioventricular
BAL	British Anti-Lewisite
BC	before Christ
bd	twice daily
BDI	Beck Depression Inventory
BH4	tetrahydrobiopterin
BIH	benign intracranial hypertension
BMI	body mass index
BP	blood pressure
BPPV	benign paroxysmal positional vertigo
BSA	bovine serum albumin; body surface area
BTX-A	botulinum toxin A
BTX-B	botulinum toxin B
CAA	cerebral amyloid angiopathy
CANOMAD	chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies

CAST	Chinese Acute Stroke Trial
CBD	corticobasal degeneration; cannabidiol
CBT	cognitive behavioural therapy
CHD	coronary heart disease
CI	confidence interval
CIBIC-Plus	Clinician's Interview-Based Impression of Change Plus Caregiver Input
CIDP	chronic inflammatory demyelinating polyradiculopathy
CK	creatine kinase
cm	centimetre
CMAP	compound muscle action potential
cmH_2O	centimetre of water
CMT2	Charcot–Marie–Tooth disease type 2
CMV	cytomegalovirus
CNS	central nervous system
COC	combined oral contraceptive
COMT	catechol-*O*-methyltransferase
COPD	chronic obstructive pulmonary disease
CoQ10	coenzyme Q10
COX	cyclo-oxygenase
COX-2	cyclo-oxygenase 2
CR	controlled release
CrCl	creatinine clearance
CRP	C-reactive protein
CS	corticosteroid
CSF	cerebrospinal fluid
CT	computed tomography
CXR	chest X-ray
3,4-DAP	3,4-diaminopyridine
DA	dopamine agonist
DADS	distal acquired demyelinating symmetric neuropathy
DAWS	dopamine agonist withdrawal syndrome
DBN	downbeat nystagmus
DBS	deep brain stimulation
DDC	dopa decarboxylase
DDI	dopa decarboxylase inhibitor
DDS	dopamine dysregulation syndrome
DEXA	dual-energy X-ray absorptiometry
DIC	disseminated intravascular coagulation
DLB	dementia with Lewy bodies

DM	dermatomyositis
DM1	myotonic dystrophy type 1
DM2	myotonic dystrophy type 2
DMD	Duchenne muscular dystrophy
DML	distal motor latency
DMPS	2,3-dimercapto-1-propane sulfonate
DMSA	dimercaptosuccinic acid
DMT	disease-modifying therapy
DNA	deoxyribonucleic acid
DOPAC	3,4-dihydroxyphenylacetic acid
DRD	dopa-responsive dystonia
DRT	dopaminergic replacement therapy
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
dTT	diluted thrombin time
DWI	diffusion-weighted imaging
EA1	episodic ataxia type 1
EA2	episodic ataxia type 2
EBV	Epstein–Barr virus
ECG	electrocardiogram
ECT	ecarin clotting time
EDSS	Expanded Disability Status Scale
EDTA	ethylenediaminetetraacetic acid
EEG	electroencephalogram
EFNS	European Federation of Neurological Societies
eGFR	estimated glomerular filtration rate
EMG	electromyography
ENS	European Neurological Society
ERT	enzyme replacement therapy
ESR	erythrocyte sedimentation rate
ESRS	European Sleep Research Society
ET	essential tremor
EU	European Union
EULAR	European League Against Rheumatism
EXPRESS	EXelon in PaRkinson's disEaSe dementia Study
FBC	full blood count
FDA	Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
ft	foot
FTD	frontotemporal dementia

FVC	forced vital capacity
g	gram
GA	general anaesthesia
GABA	gamma-aminobutyric acid
GAD	glutamic acid decarboxylase
GAG	glycosaminoglycan
GBM	glioblastoma multiforme
GBS	Guillain–Barré syndrome
GC	glucocorticoid
GCA	giant cell arteritis
GDS	Geriatric Depression Scale
GMP	guanosine monophosphate
GnRH	gonadotrophin-releasing hormone
GON	greater occipital nerve
G6PD	glucose-6-phosphate dehydrogenase
GPi	globus pallidus internus
GTN	glyceryl trinitrate
5-HIAA	5-hydroxyindoleacetic acid
5HT	5-hydroxytryptamine
h	hour
HAART	highly active antiretroviral therapy
HbA1c	glycated haemoglobin
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HC	hemicrania continua
HCT	haematopoietic cell transplantation
HD	Huntington's disease
HDL	high-density lipoprotein
HERG	human ether-a-go-go related gene
HHV	human herpesvirus
HIV	human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA
HPA	hyperphenylalaninaemia
HPS	Heart Protection Study (trial)
hs-CRP	high-sensitivity C-reactive protein
HSV	herpes simplex virus
HUS	haemolytic uraemic syndrome
HVA	homovanillic acid
Hz	hertz
IASP	International Association for the Study of Pain

IBM	inclusion body myositis
ICD	impulse control disorder
ICH	intracerebral haemorrhage
ICP	intracranial pressure
ICSD-2	International Classification of Sleep Disorders, second edition
ICU	intensive care unit
IFCC	International Federation of Clinical Chemistry
IFN	interferon
IgG	immunoglobulin G
IgM	immunoglobulin M
IHS	International Headache Society
IIH	idiopathic intracranial hypertension
IL	interleukin
ILAE	International League Against Epilepsy
IM	intramuscular
INR	international normalized ratio
INTERACT	Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial
IQ	intelligence quotient
IR	immediate release
IRIS	immune reconstitution inflammatory syndrome
IRLS	International Restless Legs Scale
ISC	intermittent self-catheterization
IST	International Stroke Trial
ITB	intrathecal baclofen
ITP	immune thrombocytopenic purpura
iu	international unit
IV	intravenous
IVIg	intravenous immunoglobulin
JCV	JC virus
KCl	potassium chloride
KF	Kayser–Fleischer
kg	kilogram
L	litre
LARGO	Lasting effect in Adjunct therapy with Rasagiline Given Once daily (study)
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LEMS	Lambert–Eaton myasthenic syndrome
LFT	liver function test

LGS	Lennox–Gastaut syndrome
LMN	lower motor neuron
LMWH	low-molecular weight heparin
LO	Lorenzo's oil
LOTS	Late Onset Treatment Study
LP	lumbar puncture
m	metre
MAG	myelin-associated glycoprotein
MAM	menstruation-associated migraine
MAO-A	monoamine oxidase A
MAO-B	monoamine oxidase B
MAOI	monoamine oxidase inhibitor
MC	mineralocorticoid
MCA	middle cerebral artery
MCI	mild cognitive impairment
MDS	International Parkinson and Movement Disorder Society
MELAS	mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes
mEq	milliequivalent
mg	milligram
MG	myasthenia gravis
MGUS	monoclonal gammopathy of undetermined significance
MHC	major histocompatibility complex
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	myocardial infarction
micromol	micromole
MIMS	Mitoxantrone in MS (study)
min	minute
mL	millilitre
MLD	metachromatic leukodystrophy
mm	millimetre
mmHg	millimetre of mercury
MMN	multifocal motor neuropathy
mmol	millimole
MMSE	mini mental state examination
MND	motor neuron disease
MOH	medication overuse headache
MPA	mycophenolic acid
MPS	mucopolysaccharidosis
MR	modified-release; magnetic resonance

MRI	magnetic resonance imaging
MRS	Modified Rankin Scale
ms	millisecond
MS	multiple sclerosis
MSA	multisystem atrophy
MTIC	monomethyl triazeno imidazole carboxamide
MUGA	multigated acquisition (scan)
MuSK	muscle-specific kinase
mV	millivolt
NA	noradrenaline
NAM	necrotizing autoimmune myopathy
NB	nota bene (take note)
NDRI	noradrenaline–dopamine reuptake inhibitor
NE	niacin equivalent
NEAD	non-epileptic attack disorder
NEDA	no evidence of disease activity
ng	nanogram
NICE	National Institute for Health and Care Excellence
NIHSS	National Institutes of Health Stroke Scale
NMDA	*N*-methyl-*D*-aspartate
NMJ	neuromuscular junction
NMO	neuromyelitis optica
nmol	nanomole
NMS	neuroleptic malignant syndrome
NNT	number needed to treat
NO	nitric oxide
NPI	Neuropsychiatric Inventory
NSAID	non-steroidal anti-inflammatory drug
OAB	overactive bladder
od	once daily
ONTT	Optic Neuritis Treatment Trial
OR	odds ratio
PACNS	primary angiitis of the central nervous system
PAH	phenylalanine hydroxylase
PAN	polyarteritis nodosa
PBG	porphobilinogen
PCNSL	primary central nervous system lymphoma
PCOS	polycystic ovary syndrome
PCP	*Pneumocystis jiroveci* pneumonia
PCR	polymerase chain reaction

PCV	procarbazine, lomustine, and vincristine (regimen)
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PDE5	phosphodiesterase 5
PDQ-39	Parkinson's disease questionnaire-39
PE	phenytoin sodium equivalent
PEEP	positive end-expiratory pressure
PEG	percutaneous endoscopic gastrostomy
PEJ	percutaneous endoscopic jejunostomy
PEMA	phenyl-ethyl malonamide
PERM	progressive encephalomyelopathy with rigidity and myoclonus
PLEX	plasma exchange
PFK	phosphofructokinase
PH	paroxysmal hemicrania
PHS	Parkinson's hyperpyrexia syndrome
PLMD	periodic limb movement disorder
PLMS	periodic limb movements of sleep
PLS	primary lateral sclerosis
PM	polymyositis
PMA	progressive muscular atrophy
PML	progressive multifocal leukoencephalopathy
PNS	peripheral nervous system
PO	per os (by mouth)
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes
PPMS	primary progressive multiple sclerosis
PRES	posterior reversible encephalopathy syndrome
PRMS	progressive–relapsing multiple sclerosis
PROMM	proximal myotonic myopathy
PSP	progressive supranuclear palsy
PTNS	percutaneous tibial nerve stimulation
qds	four times daily
RBD	REM sleep behaviour disorder
RCT	randomized controlled trial
RCVS	reversible cerebral vasoconstriction syndrome
RDA	recommended dietary allowance
REM	rapid eye movement
rFVIIa	recombinant factor VIIa
RLS	restless legs syndrome
RNA	ribonucleic acid

RR	relative risk
RRMS	relapsing–remitting multiple sclerosis
rt-PA	recombinant tissue plasminogen activator
s	second
SACD	subacute combined degeneration of the cord
SAH	subarachnoid haemorrhage
SANAD	Standard And New Antiepileptic Drugs (study)
SC	subcutaneous
SCA	spinocerebellar ataxia
SCLC	small cell lung cancer
SD	standard deviation
SIADH	syndrome of inappropriate antidiuretic hormone
SLE	systemic lupus erythematosus
SMD	standardized mean difference
SNAP-25	synaptosome-associated protein-25
SNRI	serotonin and noradrenaline reuptake inhibitor
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels (trial)
SPMS	secondary progressive multiple sclerosis
spp.	species
SRT	stereotactic radiosurgical technique
SSRI	selective serotonin reuptake inhibitor
STN	subthalamic nucleus
SUNCT	short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing
TA	tranexamic acid
TAC	trigeminal autonomic cephalalgia
TAN	tropical ataxic neuropathy
TB	tuberculosis
TBZ	tetrabenazine
TCA	tricyclic antidepressant
tds	three times daily
TEN	toxic epidermal necrolysis
TFT	thyroid function test
Th2	T helper 2
THC	delta-9-tetrahydrocannabinol
TIA	transient ischaemic attack
TM	transverse myelitis
T_{max}	maximum plasma concentration
TNF	tumour necrosis factor
TOP	Tysabri Observational Program

t-PA	tissue plasminogen activator
TPMT	thiopurine methyltransferase
tRNA	transfer ribonucleic acid
TS	Tourette's syndrome
TTH	tension-type headache
TTP	thrombotic thrombocytopenic purpura
U&E	urea and electrolytes
UHDRS	Unified Huntington's Disease Rating Scale
UK	United Kingdom
UMN	upper motor neuron
UPDRS	Unified Parkinson's Disease Rating Scale
USA	United States
UTI	urinary tract infection
VaD	vascular dementia
VAMP	vesicle-associated membrane protein
VAS	visual analogue scale
VCAM-1	vascular cell adhesion molecule 1
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VGCC	voltage-gated calcium channel
Vim	ventralis intermedius
VIM	ventral intermediate
VKORC-1	vitamin K epoxide reductase complex-1
VLCFA	very-long-chain fatty acid
VLDL	very-low-density lipoprotein
VMAT2	type 2 vesicular monoamine transporter
VOR	vestibulo-ocular reflex
vs	versus
VTE	venous thromboembolism
VZV	varicella-zoster virus
WBC	white blood cell
WCC	white cell count
WD	Wilson's disease
WE	Wernicke's encephalopathy
WHO	World Health Organization
WMD	weighted mean difference
w/v	weight by volume
w/w	weight by weight
YGTSS	Yale Global Tic Severity Scale

How to use this book

Drugs in Neurology includes clinical and prescribing information for over 180 drugs. It is split into two sections. The first half of the book contains chapters covering the major neurological sub-specialties and common neurological symptoms. The second half comprises individual drug monographs for all the major agents used in neurology, listed in an easily accessible A–Z format.

In the sub-specialty chapters, all treatable conditions likely to be encountered in adult neurological practice are included. A brief discussion of core clinical features, all recommended treatments, and a synthesis of the evidence base for each treatment are outlined for each condition.

In the A–Z section, monographs are provided for individual drugs and also for relevant drug classes. Each monograph contains licensing information (UK, USA, and off-license uses), details of available formulations (generic and brands), and mechanism(s) of action.

Toxicity and side effects are outlined in the individual drug sections, or in the associated drug class monographs if they are shared with other similar drugs. Common and severe side effects are highlighted, but side effects considered both common and severe are placed only in the severe category to avoid duplication. Dose adjustments or restrictions recommended in renal and hepatic impairment, the elderly, pregnancy, and breastfeeding are also included.

Efficacy data are given, along with the evidence base for each condition, with a focus on key trials and meta-analyses, which are referenced. Where evidence is lacking, this is stated. Finally, practical information facilitating safe use of the medication is provided. This includes dosing and monitoring guidelines, and details of pharmacokinetics and interactions.

Disclaimer

Every effort has been made to ensure the accuracy of the information presented within this text, with use of manufacturers' guidance, official guidelines, and recognized drug formularies such as the *British National Formulary*. However, the text should not be used as a substitute to the most up-to-date published guidance, and national and local formularies.

Section 1

Clinical conditions

Chapter 1

Headache

Introduction

Headache is one of the commonest neurological presentations to primary care and neurology clinics. It accounts for an estimated 4.4% of general practice consultations and 2.2% of emergency department visits.

Classification

The International Headache Society (IHS) classification for headache (ICHD-2) considers headache disorders to be either primary or secondary. Primary headache disorders include migraine, tension-type headache (TTH), and trigeminal autonomic cephalalgias (TACs). Secondary headache disorders are conditions in which headache arises due to an underlying identifiable cause. Medication overuse headache (MOH) is the most commonly encountered secondary headache in clinical practice.

Headaches

Headaches can be broadly categorized into three groups:

- Primary headache syndromes include:
  1. migraine with and without aura;
  2. TTH;
  3. cluster headache and other TACs, e.g. paroxysmal hemicrania (PH), hemicrania continua (HC), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT);
  4. other primary headaches, e.g. primary cough, exertional, stabbing and thunderclap headaches, and headache associated with sexual activity.
- Secondary headache syndromes include:
  1. headaches secondary to head and neck pathology;
  2. substance use or its withdrawal, e.g. MOH;
  3. psychiatric disorder.
- Cranial neuralgias and facial pain, e.g. trigeminal neuralgia.

This chapter will deal with the symptomatic treatment of primary headache syndromes, idiopathic intracranial hypertension, and MOH. Trigeminal neuralgia is discussed in Chapter 5, Neuropathic pain.

General principles of treatment

1. *Headache diaries and regular review*: patients should be encouraged to keep headache diaries in order to find associations with previously unknown triggers and to assess medication efficacy. They should also be regularly reviewed to assess efficacy of treatment and side effects of drugs used.
2. *Acute treatment of headache attacks*: treatment should be initiated as early as possible in the attack. The analgesic agents used should be appropriate for the severity of the headache, and be effective and acceptable to the patient.
3. *Prevention of headache attacks*: preventative treatment should be initiated in consultation with the patient. This is typically started when quality of life is impaired, e.g. headache frequency is >2 attacks per month, there is severe or prolonged aura, or acute treatment is ineffective. The agent used depends upon patient choice, co-morbidities, and the risk of drug interactions. Treatment should be started with a proposed duration in mind, typically 3–6 months.
4. *Mini-prophylaxis/pre-emptive treatment*: patients with specific predictable triggers for headache, e.g. menstruation-associated migraine (MAM), exercise-induced migraine, will benefit from mini-prophylaxis taken prior to the trigger, e.g. non-steroidal anti-inflammatory drugs (NSAIDs) or triptans.
5. *Beware of MOH* (see Medication overuse headache, pp. 14–5): all acute abortive headache treatments are associated with MOH.

Primary headache

The American Headache Society (AHS)/American Academy of Neurology (AAN), European Federation of Neurological Societies (EFNS), and National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) have outlined recommendations for the management of common headache disorders. The following pages will focus on the primary headaches, IIH and MOH, as these are the most commonly encountered.

Migraine with or without aura

Migraine is a common headache disorder, with an estimated 324 million people affected worldwide. It affects 18% of women and 5% of men in developed countries. In adults, it is typically unilateral but can be bilateral. It is moderate to severe in intensity, has an insidious onset over minutes to hours, and is described as pulsating or throbbing. It can be associated with photophobia, phonophobia, nausea, and vomiting. Aura, a constellation of focal neurological symptoms, typically visual, sensory, or motor, if present, usually precedes the onset of headache but may occur during or after the headache attack.

Acute treatment of episodic migraine

- First line: aspirin, oral triptan, NSAID, or paracetamol.
- Second line: Non-oral triptan or combination therapy.
- If treatment failure with the above, ergot alkaloids may be used.
- Drugs to avoid: opioids.
- Adjuncts: prokinetic agents, e.g. metoclopramide or domperidone, should be given if there is nausea/vomiting or suspicion of significant absorption delay due to gastric stasis.

Evidence base

(For comparisons, see Triptans monograph, pp. 354–61.)

A large meta-analysis (53 trials) of oral triptans in migraine treatment found that almotriptan (12.5mg), eletriptan (80mg), and rizatriptan (10mg) were more effective and consistent than sumatriptan in reducing headache severity, but that eletriptan at this dose was less well tolerated; 59% of patients had a significant improvement in headache at 2h with sumatriptan 100mg. In a further meta-analysis (13 trials) of metoclopramide in acute migraine, intravenous (IV) metoclopramide was found to be more effective than placebo at reducing headache severity. There are no combined studies comparing different NSAIDs in migraine, but each individual NSAID has been shown to be superior to placebo in reducing headache severity in randomized controlled trials (RCTs). Paracetamol 1g has been shown to be effective in reducing headache pain and the symptoms of photophobia and phonophobia, compared with placebo, with about 58% of patients responding to paracetamol. Ergot alkaloids (dihydroergotamine and ergotamine) are less effective than triptans. There is some RCT evidence showing efficacy for ergotamines, but their use is limited by side effects. They may have a role in patients with prolonged migraine and a high rate of headache recurrence.

Recommendations

1. The most cost-effective triptan should be chosen first. If there is no response, despite optimum administration, then an alternative triptan should be used. Triptans are usually given at the onset of headache, and not during aura.
2. Any of the NSAIDs may be used for acute migraine. If there is failure of response with one, an alternative should be used.

Mini-prophylaxis for menstruation-associated migraine

- First line: Short course frovatriptan or NSAID.
- Second line: naratriptan or zolmitriptan.

Evidence base

Frovatriptan is the most effective triptan in mini-prophylaxis for MAM. The twice-daily (bd) dose (2.5mg bd started 2 days before menstruation and continued for a total of 6 days) has been shown in an RCT to be significantly more effective than placebo at reducing headache frequency (incidence of migraine after 6 days of use, 41% vs 67%, respectively). Naratriptan (1mg bd for 5 days) and zolmitriptan (2.5mg bd/three times daily (tds) for 7 days) have also been shown in two RCTs to be effective in MAM.

Preventative treatment for episodic migraine

Individual practice varies. The following is drawn from the guidelines.

- First line: metoprolol, propranolol, topiramate, or sodium valproate.
- Propranolol may be preferred in women of childbearing age, due to the risk of teratogenicity with topiramate and valproate.
- Second line: acupuncture, amitriptyline, flunarizine, or pizotifen.
- Third line: if treatment failure with the above, suggest candesartan, duloxetine, gabapentin, magnesium, methysergide, or venlafaxine.
- Migraine prophylaxis is deemed successful when headache attacks fall by at least 50% in 3 months.

Evidence base

The β-blockers metoprolol and propranolol have been shown in several RCTs to be effective in migraine prophylaxis. In a meta-analysis, propranolol was shown to result in a 44% reduction in migraine frequency. Topiramate has been shown to be as effective as propranolol and valproate in reducing headache frequency. In a Cochrane review of acupuncture in migraine prophylaxis (22 trials), acupuncture was found to be as effective, if not more so, than prophylactic drug treatment and produced fewer adverse effects. However, there appears to be a significant placebo effect, as no significant difference was shown in efficacy between true and sham acupuncture. In a Cochrane review, lamotrigine was found to be ineffective as a prophylactic agent in migraine.

Preventative treatment for chronic migraine

Chronic migraine is defined by the IHS as migraine headache on at least 15 days per month, for >3 months, in the absence of MOH.

Treatment

- First line: as for preventative treatment for episodic migraine.
- Second line: botulinum toxin type A.

Evidence base

There is a paucity of evidence for the pharmacological treatment of chronic migraine. In the UK, botulinum toxin is recommended after failure of three pharmacological prophylactic treatments. The PREEMPT trials (1 and 2) were RCTs assessing botulinum toxin type A in chronic migraine in patients aged 18–65 years. The pooled analysis of both studies found that botulinum toxin type A was significantly more effective than placebo at reducing the number of headache days. However, it was not effective at reducing the amount of acute analgesia taken compared with placebo.

Status migrainosus

- Definition: a severe migraine attack lasting longer than 72h.

Treatment

There is little evidence to guide treatment for status migrainosus. Possible treatments include:

- first line: IV/high-dose PO aspirin and/or IV metoclopramide, or SC sumatriptan;
- if treatment failure with above, clinicians can trial: dihydroergotamine 2mg nasal spray or suppository, diclofenac at 75mg IM, chlorpromazine 25–50mg IV or IM, prochlorperazine 12.5mg IV or IM, or prednisolone at 50–100mg PO.

Evidence base

IV aspirin and SC sumatriptan have both been shown to be effective in acute migraine in an RCT comparing them with placebo. Sumatriptan was more effective than aspirin but was associated with more adverse effects. Placebo-controlled trials have failed to show efficacy for corticosteroids in aborting migraine attacks or in reducing recurrence, but expert opinion suggests steroid use can be effective in severe migraine. Dihydroergotamine has been shown to be effective in open-label studies and is supported by expert opinion.

Tension-type headache

TTH is the commonest headache type, with a lifetime prevalence of 42% in men and 49% in women. Although a separate disorder in the IHS classification, there are many similarities between migraine and TTH, and some experts consider them phenotypically distinct manifestations of the same disorder. TTH is typically bilateral and is described as a 'tightening' or 'pressure'. It can be associated with muscle tenderness around the head and neck and with nocturnal bruxism.

Acute treatment of tension-type headache

- First line: NSAIDs and/or paracetamol.
- Second line: a combination of NSAIDs or paracetamol with caffeine.
- Drugs to avoid: opioids and triptans.
- Also consider: electromyography (EMG) biofeedback, cognitive behavioural therapy (CBT), and relaxation therapy.

Evidence base

Paracetamol 1000mg has been found in most studies to be more effective than placebo at achieving the primary outcome of freedom from pain at 2h. Aspirin, diclofenac, and ibuprofen are also consistently more effective than placebo. Paracetamol and NSAIDs have a similar efficacy in TTH, with no significant difference in adverse events. The efficacy of NSAIDs and paracetamol in TTH has been shown to be increased by a combination with caffeine (64–200mg). However, given the theoretical risk of caffeine withdrawal headache, this should be used as second-line therapy in TTH. Opioids increase the risk of MOH and should be avoided in TTH. Triptans have been shown to be effective in interval headache in patients with migraine, but efficacy in TTH has not been consistently demonstrated. EMG biofeedback has been shown in a meta-analysis to have a moderate effect in TTH, and the effect was increased when used in combination with relaxation therapy. CBT has been shown to be more effective than placebo.

Treatment of chronic tension-type headache

- First line: acupuncture or amitriptyline.
- Second line: mirtazapine or venlafaxine.

Evidence base

Amitriptyline has been shown to be consistently effective as a prophylactic agent in several RCTs, with about 40% of patients showing significant improvement in headache severity in one trial. Mirtazapine at doses used for depression has been demonstrated to be effective in patients who have not responded to amitriptyline and so may be useful in patients with TTH and co-morbid depression. An RCT of venlafaxine (150mg/day) showed efficacy in reducing headache days in patients with episodic and chronic TTH. A Cochrane review concluded that acupuncture could be useful for TTH, showing benefit in headache and pain reduction up to 3 months after treatment. Trials investigating the use of occipital nerve block and botulinum toxin injection have not demonstrated their effectiveness in the management of TTH.

Trigeminal autonomic cephalalgias

TACs are a group of primary headache disorders that comprise unilateral trigeminal pain with autonomic features such as lacrimation and rhinorrhoea. This group includes cluster headache, PH, HC, and SUNCT. Although subtle differences exist between each disorder, a common pathophysiological mechanism is implicated, with abnormal activation of the trigeminal–parasympathetic reflex and centres controlling circadian rhythms, resulting in:

- trigeminal pain;
- rhythmicity;
- autonomic dysfunction.

Cluster headache

Cluster headache is characterized by severe unilateral attacks of orbital/supraorbital/temporal pain, associated with restlessness and cranial

autonomic features (ptosis, miosis, conjunctival injection, lacrimation, nasal congestion, rhinorrhoea). The attacks are short-lived (lasting from 15min to 3h), and patients may experience up to eight attacks a day. Commonly, the attacks occur at the same time every day, often waking the patient at night. In the episodic form, there are periods of remission, lasting months to years, while, in the chronic form, there are not.

Acute treatment

- First line: high-flow oxygen (100% oxygen at 10–15L/min for 10–20min with a non-rebreathe mask) and/or nasal or SC triptan.
- Second line: intranasal lidocaine, SC octreotide, or oral zolmitriptan.
- Drugs to avoid: ergots, hyperbaric oxygen, and opioids.

Evidence base

Oxygen has been shown in RCTs to be significantly more effective than placebo at reducing cluster headache severity. A double-blind, randomized, placebo-controlled cross-over trial of 109 patients with cluster headache found that treatment with high-flow oxygen (12L/min) at the beginning of a cluster headache attack was more likely to result in the patient being pain-free at 15min than with placebo (78% vs 20%; p <0.001). Sumatriptan 6mg SC was identified as being more effective than placebo at reducing headache at 15min from moderate/severe to mild/no pain. It has been shown to be effective in about 75% of patients treated, terminating attacks within 20min. Intranasal lidocaine, SC octreotide, sumatriptan nasal spray, and oral and nasal forms of zolmitriptan are also more effective than placebo at reducing cluster headache intensity.

Transitional therapy (mini-prophylaxis)

- First line: corticosteroids or greater occipital nerve (GON) blockade.

Evidence base

- Corticosteroids have been shown to be effective as a bridging therapy for the initiation of preventative treatment. They are used for 2–3 weeks at doses of ≥30mg/day prednisone or 4mg bd dexamethasone. There is a high risk of headache recurrence with dose tapering, and so steroids should only be reduced and stopped once prophylactic agents are at therapeutic dosages.
- In severe intractable cluster headache, invasive measures, such as hypothalamic deep brain stimulation (DBS) and GON blockade, have shown promise in studies with adult patients.

Prophylactic treatment

- First line: verapamil.
- Second line: lithium, methysergide, or topiramate.
- If treatment failure with the above: baclofen, gabapentin, intranasal capsaicin, melatonin, pizotifen, or valproate.

Evidence base

Verapamil is the first-choice agent for episodic and chronic cluster headache prophylaxis. It has been shown in RCTs to be more effective than placebo at reducing cluster headache frequency. In one randomized, placebo-controlled trial, 80% of those treated with verapamil responded with a reduction in cluster headache frequency, half within the first week. Verapamil and lithium appear to have similar efficacy in reducing attacks in RCTs, but verapamil has a faster onset of action and has fewer drug interactions, and so is preferred. Open-label studies suggest that methysergide and topiramate may be effective prophylactic agents, but they have not been assessed in RCTs.

Paroxysmal hemicrania and hemicrania continua

PH is a rare headache disorder, characterized by unilateral attacks of severe head pain associated with autonomic features. It differs from cluster headache in that attacks are usually shorter in duration, lasting between 2min and 30min, and more frequent, occurring >5 times per day. It is classically highly responsive to indometacin. HC is another TAC which is highly responsive to indometacin. It is also unilateral and associated with autonomic features, but is continuous in nature with the majority of patients suffering from unremitting pain.

Treatment

- First line: indometacin.
- Second line: other NSAIDs or verapamil.
- If treatment failure with the above: ergots or topiramate.

Evidence base

Indometacin is so effective in terminating PH and HC attacks that a response to indometacin (recommended starting dose 75mg/day) is part of the diagnostic criteria. Verapamil and some other NSAIDs (piroxicam, aspirin, cyclo-oxygenase 2 (COX-2) inhibitors) appear to have some efficacy in PH in open-label studies.

Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

SUNCT is characterized by very short, severe, unilateral attacks of headache, centred around the ophthalmic trigeminal area, associated with conjunctival injection and watering. It is a rare disorder and is typically seen in middle and older age (40–70 years). Triggers for an attack include any action which stimulates an area within the trigeminal-innervated zone, e.g. brushing hair, eating, or talking. The disorder is so rare that there are no published placebo-controlled trials of treatment.

Acute treatment

- First line: IV lidocaine 1–4mg/kg/h, given for a maximum of 7 days, or IV phenytoin 250mg as a single dose.
- If treatment failure with the above: corticosteroids.

Evidence base

IV lidocaine has been shown to have inconsistent efficacy in the acute treatment of SUNCT attacks. Some case reports describe IV lidocaine aborting attacks for a few hours to weeks. Other case reports show no effect. IV phenytoin was found to be effective in terminating SUNCT in a single case report. Corticosteroids may have some effect in treating SUNCT, but consistent evidence is lacking. The doses stated above are taken from published reports.

Preventative treatment

- First line: lamotrigine 100–200 mg/day.
- Second line: carbamazepine (900mg/day), oxcarbamazepine (300mg bd), gabapentin (600–900mg/day), or topiramate (75mg/day).

Evidence base

- Lamotrigine has been shown in case series to be effective as a prophylactic agent in SUNCT. There is some evidence for efficacy of oxcarbamazepine, gabapentin, and topiramate as prophylactic agents from case reports. About one-third of patients treated with carbamazepine responded to treatment. No treatment has been shown to be consistently effective in SUNCT. The doses stated above are taken from published reports.

Hypothalamic DBS, occipital nerve stimulation, and microvascular decompression of the trigeminal nerve may have a role in some patients with refractory symptoms.

Other indometacin-responsive headache syndromes

In addition to PH and HC discussed above, other headache types which may respond well to indometacin include Valsalva-induced headache, primary cough headache, primary exertional headache, primary headache associated with sexual activity, primary stabbing headache, and hypnic headache.

- First line: indometacin.

Evidence base

All of the above disorders are sensitive to indometacin to varying degrees. The recommended starting dose is 75mg (increased to 150mg daily, according to response). PH and HC are usually consistently responsive to indometacin. Hypnic headache may also respond to lithium and caffeine, as described in case reports.

Secondary headache

In this chapter, only IIH and MOH will be discussed.

Idiopathic intracranial hypertension

IIH typically occurs in women who are overweight and of childbearing age. It is also associated with excessive vitamin A intake, growth hormone therapy, and tetracycline antibiotics, and has been linked with certain systemic illnesses, including systemic lupus erythematosus (SLE), hypoparathyroidism, sleep apnoea, and polycystic ovary syndrome (PCOS). Patients usually present with a diffuse headache, worse in the morning and on lying down and exacerbated by the Valsalva manoeuvre. They may also experience nausea, vomiting, and visual disturbances, including diplopia and obscurations, and can have papilloedema. Treatment is aimed at reducing the intracranial pressure (ICP) and reducing the risk of permanent optic nerve damage.

Management

- First line: acetazolamide.
- Other drugs to consider: corticosteroids, loop diuretics, topiramate.
- Other management strategies: repeated lumbar puncture (LP), surgery including lumboperitoneal shunting and optic nerve sheath fenestration.

Evidence base

Acetazolamide has been shown in the IIH treatment trial, an RCT, to significantly improve visual function, papilloedema grade, as well as reducing weight when compared with placebo at six months with mean doses of 2.5g/day (19% withdrawing from the trial due to adverse effects—all except one of whom took acetazolamide). The addition of furosemide has been shown to be effective in reducing pressure and papilloedema in case series. Topiramate has some carbonic anhydrase activity and is associated with weight loss, which makes it an attractive option for IIH. It has been shown to have a similar efficacy to acetazolamide in one comparative study, but more robust evidence is lacking. Due to the associated weight gain, corticosteroids are not recommended for the long-term management of IIH but can be used in bridging therapy for surgery.

Medication overuse headache

MOH occurs in patients with primary headache disorders who take acute analgesic medication regularly for >3 months. The culprit agents are:

- ergots, opioids, and triptans for ≥10 days per month;
- aspirin, NSAIDs, and paracetamol, alone or in combination for ≥15 days per month.

Management

The offending analgesic should be withdrawn. Simple analgesics can be abruptly stopped, while opioids, benzodiazepines, and barbiturates will require gradual dose reduction with close monitoring. The majority of patients can be managed in the community, but a proportion may benefit from admission and IV hydration.

If drug treatment is also required:

- first-line treatment: topiramate 100–200mg/day;
- second-line treatment: amitriptyline (up to 50mg/day), corticosteroids (up to 60mg/day), or NSAIDs.

Evidence base

Topiramate has been found to be effective in reducing headache frequency in MOH in three RCTs. Corticosteroids have shown conflicting results in MOH. One RCT showed no efficacy with 60mg prednisolone, while another found that treatment with 100mg prednisolone significantly shortened headache duration, compared to placebo. Hence, potentially a higher dose of prednisolone is needed. Amitriptyline may be effective in MOH but has not been assessed in placebo-controlled trials. NSAIDs have been used for MOH but are not first-line, as they can also cause MOH. Naproxen has been shown in one uncontrolled study to be effective in reducing intake of analgesics and headache severity when combined with amitriptyline.

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Chapter 2

Vertigo

Introduction

Dizziness accounts for over 20% of general practice visits, and 4% of accident and emergency (A&E) attendances, in the UK. It is associated with anxiety, handicap, and avoidance behaviour, resulting in significant functional impairment. Dizziness also constitutes a challenge for the physician, as both establishing a diagnosis and achieving adequate symptom control can be difficult. The word dizziness is used by patients to describe a variety of complaints, ranging from imbalance to true vertigo, light-headedness, and even headache. Therefore, one first needs to establish what the patient means by the term 'dizziness'. Patients may find this difficult, and use of analogies, such as 'spinning like a merry-go-round', 'rocking as if on a boat', off-balance, lightheaded, or faint, may help the patient to describe more accurately their symptoms.

Vertigo, when strictly defined as an illusion of either oneself or the environment moving, is a reliable symptom. It indicates involvement of the semicircular canals and/or their central projections. Localizing the exact site of the lesion relies upon the presence of associated symptoms and clinical signs. One approach is to begin by distinguishing peripheral from central vertigo. Another is to consider the commoner diagnoses first.

Peripheral vertigo is generally positional, associated with constitutional upset, nausea, and vomiting, and either occurs in isolation or in association with hearing loss and/or tinnitus. Central vertigo is rarely an isolated symptom and is often accompanied by dysarthria, paraesthesiae or weakness, diplopia, incoordination, or other brainstem or cerebellar symptoms.

The commonest causes of dizziness in general practice are benign paroxysmal positional vertigo (BPPV), postural hypotension, vestibular neuronitis/labyrinthitis, and vestibular migraine. Rarer causes include posterior circulation (brainstem or cerebellar) stroke, multiple sclerosis (MS), and Ménière's disease.

This chapter covers the evidence-based treatment options, where available, for the commoner peripheral and central vestibular disorders. It should be noted that recent evidence supports the clinical finding that traditional 'vestibular sedatives', e.g. antidopaminergics and antihistamines, have no effect on vestibulo-ocular function or the perception of self-motion and that their effect is primarily antiemetic.

Classification

The International Classification of Vestibular Disorders defines vertigo as 'The sensation of self-motion when no motion is present or altered sensation of motion when motion occurs'. Sub-classification of vertigo is difficult, and no strict universally acknowledged system, as yet, exists. Vertigo is often split on the basis of the character of the vertigo symptoms or underlying aetiology.

Classification by vertigo character

In simple terms, vertigo can be spontaneous or triggered. Spontaneous vertigo occurs without any internal or external perturbation. The main types of triggered vertigo are tabulated in Table 2.1.

Classification by vertigo aetiology

The causes of vertigo can be divided into peripheral and central types, as described in Table 2.2.

Table 2.1 Examples of triggered vertigo

Trigger	Definition
Positional	Occurs after a change in head position
Head motion	Occurs during head movement
Visually induced	Induced by busy visual environments or full-field motion (such as a train coming into the station while standing on the platform, or walking along a supermarket aisle)
Sound-induced	Auditory stimuli induce vertigo (Tullio phenomenon)
Valsalva-induced	Any bodily manoeuvre that increases intracranial or middle ear pressure
Orthostatic	Due to change in body posture from sitting or lying to standing
Other	For example, dehydration, medication, environmental pressure changes, exercise, hormones, and hyperventilation

Table 2.2 Peripheral and central causes of vertigo

Peripheral	Central
Acoustic neuroma	Posterior circulation stroke
BPPV	Episodic ataxias
Ménière's disease	Migrainous vertigo
Vestibular neuronitis/labyrinthitis	MS
Vestibular paroxysmia	

Peripheral causes of vertigo

Benign paroxysmal positional vertigo

While BPPV is the commonest cause of peripheral vertigo, accounting for 20% of all cases, it remains under-diagnosed, particularly among the elderly population whose description of 'dizziness' may be more vague.

BPPV is caused by calcium carbonate crystals (otoconia or canaliths) settling within the endolymphatic fluid of one or more semicircular canals, commonly the posterior semicircular canal. Horizontal canal BPPV is much less common, responsible for only 10–20% of cases, and anterior canal BPPV causes 5%. Although it is usually idiopathic, BPPV may be caused by head trauma or follow vestibular neuronitis. BPPV following head trauma is often bilateral.

Patients with BPPV present with violent attacks of vertigo (typically seeing the room spin), triggered by a specific and reproducible change in head position. These last only seconds, but patients may report longer duration, such is its severity and the inaccuracy of subjective recall of time. Attacks abate if the head is kept completely still, but a change of position, often in an attempt to stop the vertigo, can provoke a further attack. Nausea is common, but vomiting is rare, given the brevity of each attack.

A history of recurrent vertigo episodes triggered by movement suggests BPPV, and the diagnosis can be confirmed with the Dix–Hallpike manoeuvre.

Treatment

- First line: Epley or Semont manoeuvres for typical posterior canal BPPV.
- Drugs to avoid: medications have no role in the treatment of BPPV and are best avoided.

Evidence base

Multiple systematic reviews and meta-analyses have confirmed that repositioning manoeuvres, such as the Epley and Semont manoeuvres, are safe and effective for treating posterior canal BPPV. One meta-analysis of nine RCTs, comparing repositioning manoeuvres to sham procedures, found that the treatment arms were more likely to demonstrate symptom resolution (odds ratio (OR) 4.6, 95% confidence interval (CI) 2.8–7.6) and a negative Dix–Hallpike test (OR 5.2, 95% CI 3.0–8.8) at the time of the first follow-up. When compared with no treatment, a separate meta-analysis of 505 patients, with a mean follow-up of 16 days, found an absolute risk reduction of 41% in those exposed to treatment (number needed to treat, NNT = 2).

There are very few RCTs assessing the efficacy of medication for the symptoms of BPPV. In one study randomizing 156 patients to either the Semont manoeuvre, flunarizine (10mg/day), or no treatment, 57.7% of those on flunarizine reported symptom resolution at 6 months, compared with 94.2% of those treated with the Semont manoeuvre and 34.6% of those who received no treatment. A further double-blind, placebo-controlled RCT in 72 patients with posterior canal BPPV suggested that

combining 24mg of betahistine with the Epley manoeuvre improved quality of life above the Epley manoeuvre alone. The underlying mechanism of this response is unclear, given that BPPV is a 'mechanical' problem, and replication of these data is required before it is incorporated into clinical practice. Lorazepam 1mg and diazepam 5mg tds did not show any difference when compared to placebo treatment in BPPV.

Vestibular neuronitis

Vestibular neuronitis, or neuritis, is an inflammatory disorder of the vestibular portion of the eighth cranial nerve of presumed viral aetiology. Its incidence is 3.5 per 100000 population, although it may be overdiagnosed and misdiagnosed. For many non-specialists, the term 'vertigo' has become synonymous with 'labyrinthitis', a label that is often attached to acute and chronic dizziness, presumed to be benign in origin. True labyrinthitis, however, refers to inflammation of the whole labyrinth (vestibular *and* cochlear parts) and is exceptionally rare in clinical practice.

Clinical features

Features of vestibular neuronitis include rapid onset of severe, persistent vertigo (hours to days). Nausea, vomiting, and imbalance are seen in virtually all cases. The clinical examination reveals spontaneous unidirectional horizontal and torsional nystagmus (with the fast phase always beating away from the affected side, irrespectively of whether the patient is looking right or left). Patients with vestibular neuritis have unilateral loss of the vestibulo-ocular reflex (VOR). The head impulse test, a direct test of the VOR, will therefore be abnormal when a small-amplitude, but fast, head rotation is performed towards the affected side.

Treatment

1. Bed rest and antiemetics (antidopaminergic or antihistaminergic agents) should be given for a maximum of 3 days.
2. Patients should be encouraged to resume physical activity as soon as possible.

Evidence base

In the UK, buccal or intramuscular (IM) prochlorperazine is indicated for the rapid relief of nausea and vomiting associated with vertigo. For less severe nausea, vomiting, and vertigo, buccal or oral prochlorperazine or antihistamines are recommended. Thereafter, the chosen medication should be taken for a maximum of 3 days. In the United States (USA), dimenhydrinate is frequently used, with an RCT suggesting that a 50mg dose is superior to lorazepam 2mg in controlling vertigo in patients with vestibular neuritis presenting to the emergency department. The IV or IM routes are preferred acutely. The risk of sedation must be balanced against symptom control. Meclizine and hyoscine are useful antiemetics and less sedating, but there is no evidence that they modulate vertigo. In addition, vestibular exercises have been shown to improve central vestibulo-spinal compensation after the acute symptoms have resolved, in a small prospective study of 39 patients.

Corticosteroids, antivirals, and benzodiazepines are not routinely used, as there is no evidence that they improve long-term outcomes.

Ménière's disease

Ménière's disease is a rare condition, with an incidence anywhere between 7.5 and 160 per 100 000, depending on the country and the diagnostic criteria used. It is caused by excess endolymphatic fluid pressure, and indeed 'endolymphatic hydrops' is the pathological hallmark of this condition. The diagnosis is made on the basis of clinical findings. The American Academy of Otolaryngology Head and Neck Surgery guidelines recommend that a diagnosis of 'definite' Ménière's disease requires two or more spontaneous episodes of vertigo, each lasting 20min or longer, hearing loss documented by audiograms on at least one occasion, tinnitus or aural fullness in the affected ear, and exclusion of other causes (typically with gadolinium-enhanced magnetic resonance imaging (MRI) of the brain).

Clinical features

Patients often present with spontaneous, episodic, disabling vertigo (lasting minutes to hours), in association with unilateral tinnitus, aural fullness, and unilateral fluctuating deafness. There is typically associated nausea and vomiting, with imbalance that may last several days. Examination will reveal horizontal torsional nystagmus in the acute phase, together with an impaired ipsilateral VOR. Some patients develop otolithic crises, termed Tumarkin attacks, leading to severe lateropulsion and falls. The symptoms may not be present simultaneously, particularly in the early phases of the disease. In one study, 50% of patients presented with contemporaneous audiovestibular loss, 19% with vertigo only, and 26% with isolated hearing loss.

The course is typically relapsing–remitting, although some patients may present with a more progressive course. In some patients, episodes occur as frequently as every few days, although more typically every few months. Spontaneous remission is recognized, although symptoms may recur later in life. Audiometric testing may reveal a low-frequency sensorineural deafness, which may fluctuate over time, and bithermal caloric testing rotational tests with electro-nystagmography may reveal a reduced unilateral vestibular response. Vestibular-evoked myogenic potentials and electro-cochleography may assist with the diagnosis but are not routinely used outside highly specialized centres.

Treatment

There is no cure for Ménière's disease; hence the aim of treatment is to reduce symptom load.

- Acute: treatment of Ménière's disease involves the control of vertigo and nausea in the acute setting with antiemetics, antihistamines, and other centrally acting sedative medication.
- Long-term treatment:
  - first line: salt restriction and diuretics;
  - second line: betahistine;
  - third line: steroids and gentamicin administered via intratympanic injection.

In clinical practice, the first-line treatments are dietary modifications with salt restriction, and the use of diuretics, typically bendroflumethiazide.

If there continue to be attacks, an increasing dose of betahistine can be tried, although, in severe attacks or where attacks are frequent, intratympanic steroids or gentamicin are preferred.

Evidence base

1. Salt restriction and diuretics: these measures have traditionally been considered the best medical therapy for Ménière's disease, reportedly controlling vertigo in 58% of patients and stabilizing hearing in 69%. The effect of diuretics has not, however, been systematically replicated.
2. Betahistine: betahistine (a weak H1 agonist and a strong H3 antagonist) has been used in the treatment of vertigo for over 50 years, with early evidence suggesting a vasodilating action on the inner ear and cerebral blood vessels. A 2001 Cochrane study reviewed its use in the treatment of vertigo but concluded that none of the trials ($n = 6$) assessed the effect of betahistine adequately, although most reported a reduction of vertigo. One observational study ($n = 112$) suggested high-dose betahistine (48mg tds) was significantly superior to 24mg tds, particularly at 12 months. Doses as high as 480mg/day have been used successfully in individual patients.
3. Intratympanic corticosteroid and gentamicin injections: there is limited evidence from small trials for the use of intratympanic membrane injections of corticosteroids and gentamicin in the treatment of Ménière's disease. Two Cochrane reviews published in 2011 looked at each medication individually. The corticosteroid review found only one placebo-controlled trial for intratympanic steroids ($n = 22$). The study showed that, after administration of 4mg/mL of intratympanic dexamethasone for 5 consecutive days, there were statistically significant improvements in vertigo, as evidenced by improved functional level (90% vs 42%), change in the Dizziness Handicap Inventory score (60.4% vs 41.3%), and mean vertigo subjective improvement (90% vs 57%), compared to placebo. These changes were maintained over a follow-up of 24 months. The Cochrane review investigating the use of intratympanic gentamicin identified two placebo-controlled trials ($n = 50$), which showed a significant reduction in vertigo with treatment. However, it was recommended that this treatment is reserved for patients with pre-existing hearing loss, as 20% will develop a degree of deafness as a complication. Likewise, it is only recommended for administration to one ear, despite around 40% of patients developing bilateral disease after 20 years. Two recent studies have compared the treatments. One cohort study, comparing intratympanic methylprednisolone with gentamicin, found that 82.9% of the gentamicin group and 48.1% of the steroid group achieved complete control of vertigo ($p = 0.004$), with better control of tinnitus and aural fullness with gentamicin than methylprednisolone ($p \leq 0.002$). The second study, a prospective RCT, showed similar results in that the frequency of vertigo attacks in refractory Ménière's disease was preferentially reduced with gentamicin (93% vs 61%).

Vestibular paroxysmia

This is a rare, but important, syndrome characterized by brief (milliseconds to seconds) attacks of vestibular and auditory deficits, including vertigo, imbalance, and tinnitus. It is thought to arise from neurovascular cross-compression of the vestibular nerve and an offending vessel. It is important to consider the diagnosis in patients presenting with paroxysmal spontaneous vertigo, as it is readily treatable.

Treatment

- First line: carbamazepine or oxcarbazepine.
- Second line: gabapentin, lamotrigine, phenytoin, or sodium valproate.
- Refractory symptoms: microvascular neurosurgical decompression of the eighth cranial nerve.

Evidence base

Where there are >2 severe episodes per month, treatment with carbamazepine 200–600mg/day may be successful. Both symptoms of tinnitus and vertigo should respond to carbamazepine, and such response is often considered part of the proposed diagnostic criteria for the condition. Antiepileptic drugs (AEDs), such as gabapentin, lamotrigine, phenytoin, and sodium valproate, are alternatives for patients who do not tolerate carbamazepine, although the evidence for these is based on case studies and expert consensus, as no RCTs have been conducted.

Central causes of vertigo

Vestibular migraine

A diagnosis of vestibular migraine is not widely recognized outside specialist practice, but approximately half of patients with classical migraine will report dizziness and vertigo, with another 20% fulfilling the criteria for migrainous vertigo. Patients with vestibular migraine commonly report spontaneous or positional vertigo lasting hours to days. The typical patient is a migraineur who has noticed a recent increase in headache frequency and, over the same period, developed vestibular episodes, with headache and vertigo not necessarily occurring together. Other migrainous features, such as photophobia, phonophobia, and nausea, are often present during the vertiginous episode, in addition to increased motion sensitivity, i.e. an aversion to self-movement and external motion.

Vestibular migraine remains a diagnosis of exclusion. The clinical examination during an attack may reveal a number of different oculomotor abnormalities (in up to 60% of cases), including nystagmus of a central type. Thus, acute brain imaging may be required on first presentation. The diagnosis is aided by a previous history of similar symptoms, or a strong personal or family history of migraine. It should be noted that BPPV, Ménière's disease, anxiety disorders, and orthostatic hypotension are commoner in migraine sufferers than in controls and may cause diagnostic confusion.

Treatment

- As per migraine (see prophylaxis of episodic migraine pp. 8–9).

Evidence base

There are no prospective controlled trials specifically investigating the treatment of vestibular migraine to date. The therapeutic recommendations for vestibular migraine are currently based on the guidelines for migraine treatment, including administration of β-blockers or amitriptyline for a period of 3–6 months. Alternatives are topiramate or valproic acid, although these have only been described in small observational studies for vestibular migraine.

Posterior circulation stroke

Posterior circulation stroke is characterized by the abrupt onset of vertigo (within seconds), often accompanied by occipital headache. Other associated signs may include gait or limb ataxia, facial numbness, Horner's syndrome, hearing loss, contralateral hemiparesis and hemisensory loss, reflecting simultaneous involvement of other cerebellar or brainstem structures. Importantly, the head impulse test remains normal in posterior circulation stroke, with the exception of rare isolated strokes mimicking a peripheral vestibulopathy. Immediate brain imaging is indicated in suspected stroke of the posterior circulation, as these patients may require thrombolysis or even surgical intervention. Red flags in cases of acute dizziness include unilateral hearing loss, other neurological symptoms or signs, new headache, and a normal VOR as assessed by the head impulse test.

Treatment

- As per stroke (see Chapter 4, Cerebrovascular disease).

Multiple sclerosis

The vestibular system is frequently involved in MS. In fact, vertigo is much commoner than hearing impairment in this group of patients. Vertigo is seen as an initial presentation in 5% of patients with MS and will ultimately occur in 40% of patients with established MS. Patients usually describe vertigo that is torsional (rotational) but can be in any direction and can be positional. Physical examination during an acute attack of vertigo often reveals spontaneous or positional nystagmus which may be of a 'central' type—persistent and without latency (in contrast to BPPV, which has a 3–4s latency and is short-lived). There may also be gait and limb ataxia, dysarthria, and slow pursuit movements related to cerebellar dysfunction.

It is important to remember that BPPV remains the commonest cause of vertigo and imbalance, irrespective of any coexisting neurological syndrome. Thus, vertigo should not be automatically attributed to demyelination in a patient with MS.

Treatment

- As per MS (see Chapter 6, Inflammatory disorders of the central nervous system).
- In the acute setting, many physicians favour the use of benzodiazepines to treat vertiginous symptoms, although there are no randomized clinical trials to guide management.

Episodic ataxias

The episodic ataxias are a group of seven dominantly inherited channelopathies, of which types 1 (EA1) and 2 (EA2) are the commonest, and result from mutations in a voltage-gated potassium channel and a brain-specific subunit of the P/Q type calcium channel, respectively. The syndrome is characterized by stress-induced attacks of ataxia and dysarthria, with signs of interictal nystagmus and late-onset progressive ataxia. ~30–50% of individuals with EA2 develop a slowly progressive cerebellar ataxia.

Treatment

- EA1: acetazolamide, carbamazepine, or sodium valproate.
- EA2:
  - first line: acetazolamide;
  - second line: aminopyridines.

Evidence base

Acetazolamide, a carbonic anhydrase inhibitor, is the drug of choice for preventing attacks of EA2, although some patients are resistant to this medication, in which case the aminopyridines can be used. There is some evidence from small trials that 4-aminopyridine (4-AP) may be more effective than equivalent doses of 3,4-diaminopyridine (3,4-DAP) for the control of downbeat nystagmus (DBN) (often observed in EA2).

Patients with EA1 have a variable response to acetazolamide; hence, carbamazepine or sodium valproate are often used on the basis of observational studies and expert consensus. There have been no controlled studies comparing the efficacy of different drugs.

Newer treatments for oscillopsia

Oscillopsia refers to the illusion of oscillation of the visual world and, in the clinical setting, denotes the presence of nystagmus. Patients with oscillopsia may describe blurring, 'wobbly', or 'jumpy' vision. Further in-depth information with regard to subtypes and aetiology is beyond the scope of this book. For a review on the causes and therapy of oscillopsia, the reader is referred to the 2004 EFNS Task Force guidance (see References, p. 27). Pharmacological treatments of oscillopsia include the following, although no double-blind clinical trials are available:

1. aminopyridines, e.g. 3,4-DAP (3 × 20mg/day) and 4-AP (3 × 10mg/day), may be used for DBN;
2. modified amino acid acetyl-DL-leucine may be used for cerebellar ataxia;
3. gabapentin, valproate, clonazepam, memantine, and biperiden can be tried for continuous (rather than positional or paroxysmal) oscillopsia. There is variable response to these drugs, so each should be tried individually before being used in combination.
4. In one case series, treatment with baclofen (5–10mg PO tds) resulted in an improvement in several patients with upbeat nystagmus.

Evidence base

Additional treatment that may be used off-licence by some specialists are the aminopyridines, a modified amino acid acetyl-DL-leucine and potassium channel blockers; 4-AP has been shown to improve the symptoms of DBN, a condition whose aetiology is commonly cerebellar degeneration or ischaemia. Fifty-seven per cent of patients in one RCT responded to treatment, as measured by tandem-walk, 'get-up-and go' tests, and measurements of visual acuity. A recent case series of 13 patients showed that the modified amino acid acetyl-DL-leucine (5g/day) exerts a significant effect on cerebellar ataxia after only 1 week.

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Chapter 3

Epilepsy

Introduction

Up to 5% of people will develop epilepsy at some point during their lifetime. It is markedly more common in those <16 years and >65 years of age. Epilepsy is not a single condition but a diverse group of disorders. There are over 30 electroclinical syndromes described and a growing number of AEDs. This chapter will focus on epilepsy in adulthood.

The International League Against Epilepsy (ILAE) defines epilepsy as: 'a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurologic, cognitive, psychological and social consequences of this condition'. A seizure is further defined as: 'a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain'.

Classification

Seizures can be divided into focal (partial) and generalized forms. Generalized seizures are further subcategorized, predominantly based on their motor features (see Fig. 3.1). These subtypes guide AED selection (see further text). Certain AEDs are preferentially used for the management of specific seizure types, e.g. ethosuximide in the treatment of absence seizures, or avoided in other seizure types, e.g. carbamazepine which can exacerbate myoclonic epilepsy. Focal seizures, although, as a group, typically treated with similar AEDs, can be subdivided based on their site of onset, pattern of spread, involvement of arousal centres and the presence or absence of secondary generalization.

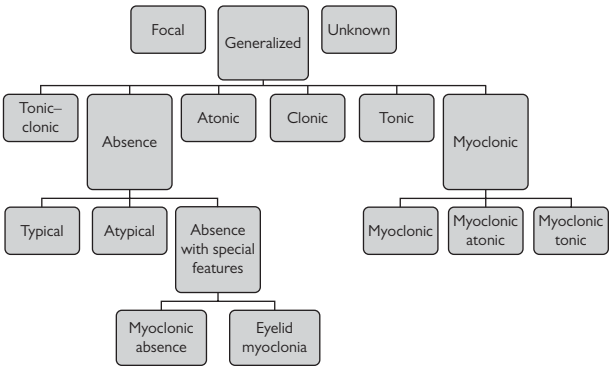

Fig. 3.1 ILAE seizure type classification.

Adapted from Epilepsia, 51(4), Berg, A. T., Berkovic, S. F., Brodie, M. J., Buchhalter, J., Cross, J. H., Van Emde Boas, W., Engel, J., French, J., Glauser, T. A., Mathern, G. W., Moshé, S. L., Nordli, D., Plouin, P. and Scheffer, I. E., Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009, pp. 676–685, Copyright (2010), with permission from John Wiley and Sons.

When to initiate treatment

Differential diagnosis Retrospective studies have shown that a large proportion of patients treated for epilepsy actually have an alternative diagnosis. Non-epileptic attack disorders (NEADs) provide the most diagnostic difficulty. Alternative diagnoses need to be explored both prior to initiation of therapy and later if seizure control proves unexpectedly difficult or variable.

First fit review Patients with a 'first fit' need a medical review, blood biochemistry, and an electrocardiogram (ECG), and the majority of adults will require imaging, preferably head MRI. Specialist review is needed prior to considering long-term AEDs.

Factors influencing when to start treatment Following an unprovoked first seizure, the chance of a second seizure within the next 2 years is >40%. Risk factors for subsequent development of epilepsy are:

- ≥2 seizures;
- underlying neurological disorder/deficit;
- abnormal electroencephalogram (EEG).

High-risk individuals with one or more of the above factors may be started on an AED from the first seizure, after careful discussion with the patient.

Individuals who have low/medium risk for seizure recurrence typically start treatment after the second seizure. The following factors direct when to initiate treatment and which specific AED to consider:

- seizure symptomatology and duration;
- psychosocial morbidity, including driving regulations;
- medical co-morbidity;
- pregnancy.

Treatment strategies

Monotherapy Single AED treatment should be used where possible. AEDs should be uptitrated to a level sufficient to control attacks or to the maximum tolerable level. If treatment is unsuccessful, then monotherapy with an alternative first- or second-line agent is recommended. The new drug should be started, and the first drug slowly tapered when the new drug is at appropriate maintenance levels. Three different agents should ideally be trialled as monotherapy, before combination therapy is initiated. Fifty per cent of patients should expect to be seizure-free on their first AED. If not, then trial of a new AED, either as monotherapy or combination therapy, should render a third of the remainder seizure-free, and, if this fails, then a third AED will render a quarter of the remainder seizure-free. This means that, in total, ~70% of patients can be expected to be seizure-free after a trial of three AEDs.

Combination therapy If monotherapy fails, it may be necessary to add an adjunct. The monotherapy agent which has proved most effective should be used with an alternative first- or second-line drug. Care needs to be taken with polytherapy, in order to ensure that potential pharmacokinetic interactions and pharmacodynamic side effects are discussed with the patient and adjusted for. There is little evidence to suggest exactly which combinations are most effective, although there are some pairings which have demonstrated a synergistic effect on seizure control, and these should be used, if possible, e.g. clonazepam and valproate in the treatment of absence seizures, and lamotrigine and valproate in the treatment of generalized seizures.

Refractory epilepsy

In adults, refractory epilepsy is defined as either:

1. failure of two or more AEDs at their optimal dosage to control seizures; or
2. continuing seizures after 2 years of treatment.

10–20% of epileptics will not be controlled sufficiently by AEDs. In these, the most effective regime should be continued. They may be candidates for epilepsy surgery, depending on the specific epilepsy disorder and the effects of the condition on the patient's quality of life. If surgery is indicated, then there may be up to 60–70% chance of epilepsy remission, with the rest usually experiencing some reduction in seizure frequency. Surgery may be resective or non-resective, depending on whether epileptogenic foci are present. Non-resective surgery can include vagus nerve stimulation, subpial transections, and corpus callostomies.

Pharmacological treatment (adapted from NICE guidelines)

Treatment of epilepsy is divided, depending upon the seizure type. Care should be taken when patients have multiple seizure types, as AEDs effective in the treatment of one seizure type may exacerbate others, e.g. carbamazepine may exacerbate absence seizures.

Focal-onset seizures

Focal epilepsies represent a varied clinical picture, including motor, sensory, autonomic, and dyscognitive phenomena, and may display secondary generalization.

Treatment

- First line: carbamazepine or lamotrigine.
- Second line: levetiracetam, oxcarbazepine, or valproate.
- Additional adjuncts: clobazam, gabapentin, perampanel, retigabine, or topiramate.
- If treatment failure with the above: acetazolamide, eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin, or zonisamide.

Evidence base

The SANAD (Standard And New Antiepileptic Drugs) study (2007) was a large unblinded RCT, based in the UK. It looked at the effectiveness of commonly used AEDs in focal-onset and generalized epilepsy. With regard to focal-onset epilepsy, it showed:

1. lamotrigine had a longer time to treatment failure than all alternatives, except for oxcarbazepine;
2. carbamazepine was significantly better than most alternative AEDs with regard to the number of patients experiencing remission at 12 months, although statistically the advantage with respect to lamotrigine was not significant.

The results suggest that lamotrigine and carbamazepine have similar efficacy at controlling seizures but that lamotrigine is better tolerated.

Generalized seizures

Absence seizures

Typical absence seizures are short episodes of loss of consciousness, usually with preserved muscle tone and little motor activity other than subtle clonic movements. *De novo* absence seizures beginning in adulthood are rare, and symptoms, if epileptic in origin, are more likely to be attributed to non-convulsive primary or secondary generalized epilepsy. Atypical variants can occur where a degree of awareness is preserved, and the EEG, although abnormal, may not be classical.

Treatment

- First line: ethosuximide or valproate.
- Second line: lamotrigine.
- If treatment failure with the above: clobazam, clonazepam, levetiracetam, phenobarbital, topiramate, or zonisamide.
- Drugs to avoid: carbamazepine, eslicarbazepine acetate, gabapentin, oxcarbazepine, pregabalin, tiagabine, and vigabatrin.

Evidence base

A large double-blind RCT conducted in the USA compared ethosuximide, valproate, and lamotrigine in the treatment of childhood absence epilepsy. The study's key findings were:

1. at 16 weeks, the freedom-from-failure rates were higher for valproate and ethosuximide than lamotrigine;
2. tolerance was similar for all three drugs;
3. attentional dysfunction was commoner with valproate than ethosuximide (49% vs 33%).

Myoclonic seizures

Myoclonic seizures are characterized by brief contractions of muscles or muscle groups. These can be singular or repetitive movements. They are often short, with little or no post-ictal stage, so that patients may not even be aware of an alteration in consciousness.

Treatment

- First line: valproate.
- Second line: levetiracetam or topiramate.
- If treatment failure with the above: clobazam, clonazepam, piracetam, or zonisamide.
- Drugs to avoid: carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, and vigabatrin.

Evidence base

The SANAD study is one of the most important sources of evidence in the treatment of juvenile myoclonic epilepsy and isolated myoclonic seizures; however, it did not separate juvenile myoclonic epilepsy from other idiopathic generalized epilepsies. There is little high-quality evidence looking specifically at first-line drugs for the treatment of myoclonic epilepsy syndromes.

Tonic–clonic seizures

These are classic convulsive seizures. The tonic phase usually lasts for ~20s and involves sustained muscular contraction with loss of consciousness. The clonic phase involves convulsive jerks of all four limbs and may be associated with respiratory arrest.

Treatment

- First line: valproate.
- Second line: lamotrigine.
- Third line: carbamazepine or oxcarbazepine.
- Additional adjuncts: clobazam, levetiracetam, or topiramate.
- If treatment failure with the above: acetazolamide, clonazepam, phenobarbital, or phenytoin.
- Drugs to avoid: tiagabine and vigabatrin.

Evidence base

A large meta-analysis incorporating eight Cochrane reviews and data from the SANAD study evaluated potential first-line agents. Valproate performed significantly better than carbamazepine, topiramate, and phenobarbital. There was a non-significant trend suggesting that valproate had a better outcome than lamotrigine, and further analysis of secondary outcomes suggested that 12-month remission levels and time to first seizure were significantly improved with valproate vs lamotrigine. There were not sufficient data to compare valproate with phenytoin; however, it was felt phenytoin had a markedly worse side effect profile.

Tonic or atonic seizures

Tonic seizures are sustained muscular contractions without a clonic phase. They are often associated with classical EEG patterns and more typical of patients with severe learning disability or diffuse cerebral damage. They are commonly present as part of Lennox–Gastaut syndrome (LGS). Atonic seizures are characterized by loss of postural control. This can occur either suddenly in the form of a drop/astatic attack where they fall to the floor, or slowly where there may be a progressive loss of tone in the limbs and neck. The astatic attacks are often short-lasting with swift recovery.

Treatment

- First line: valproate.
- Additional adjuncts: lamotrigine.
- If treatment failure with the above: acetazolamide, clobazam, clonazepam, levetiracetam, phenobarbital, rufinamide, or topiramate.
- Drugs to avoid: carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine, and vigabatrin.

Evidence base

Most of the evidence is extrapolated from knowledge of AED effectiveness in other generalized epilepsy syndromes, in combination with expert opinion.

Antiepileptic drugs in young women

Pregnancy

Pregnancy typically has little impact on the rate of seizures for most women. A minority, particularly those with severe epilepsy, find that their seizures worsen (17%), while others find that their seizures decrease or cease altogether (16%). Seizure frequency may change due to changes in plasma levels of AEDs caused by changes in gastric motility, plasma proteins, plasma volume, hepatic and renal function, and volume of distribution. In addition, vomiting, stress, sleep deprivation, and inappropriate dose reductions by doctors or by patients themselves alarmed about the teratogenic potential may all contribute.

The risks of poorly controlled epilepsy in pregnancy include risk of trauma to the feto-placental unit during convulsions, as well as a 50% fetal, and 30% maternal, risk of mortality if status epilepticus develops. Hence, in some instances where plasma AED levels drop in pregnancy, AED doses may have to be increased temporarily.

Labour

AEDs should be given as normal during labour; if this is not possible, an alternative method of enteral/parenteral administration should be used. One to 2% of patients with epilepsy will have tonic–clonic convulsions during delivery. Patients with epilepsy should ideally give birth in hospital, with continuous fetal monitoring. In patients particularly at risk of seizures, a prophylactic 10–20mg of clobazam can be given in the early stages of labour. If the risks are too great, then a Caesarean section should be considered. Prolonged seizures and status during pregnancy should be treated as for other adults. Neonates are very susceptible to respiratory depression.

Effects on the fetus of antiepileptic drug use during pregnancy

Major congenital malformations

AED usage during pregnancy is associated with teratogenicity. This has been confirmed in several human observational studies for many of the older drugs. Animal studies have suggested that most new AEDs may also have teratogenic potential. The background rate of teratogenicity in the normal population is ~2%. Major congenital malformations occur in ~4–7% of patients on AEDs (see Table 3.1) and 3.5% of patients with epilepsy not on AEDs. The likelihood of congenital malformations is higher with high doses of AEDs, multiple AEDs, and specific AEDs, e.g. valproate.

Fetal anticonvulsant syndromes and reduced cognitive function

The presence of fetal anticonvulsant syndromes is controversial. Fetal carbamazepine, phenobarbital, phenytoin, primidone, and valproate syndromes have all been described. They involve characteristic patterns of dysmorphism, e.g. growth delay, finger hypoplasia, and even an increased risk of neuroblastoma with phenytoin use. The syndromes are difficult to prove, as the features described have a large degree of overlap with the normal population. In addition, a large study conducted in 2009 suggested

Table 3.1 The rate of major malformations with AED monotherapy in pregnancy.

AED	Teratogenicity	Main associated major malformations
Carbamazepine	2.2%	Cardiac and facial cleft
Lamotrigine	3.2%	Cardiac, GI and GU
Phenobarbital	>CBZ, <PHT	Cardiac
Phenytoin	3.7%	Cardiac, facial cleft and GI
Topiramate	7.1%	Facial cleft and GU
Valproate	6.2%	Cardiac, facial cleft, GU, neural tube defects and skeletal

CBZ, carbamazepine; GI, gastrointestinal; GU, genitourinary; PHT, phenytoin.

that children exposed to valproate *in utero* had an intelligence quotient (IQ) 9 points lower than children who were exposed to other AEDs, e.g. lamotrigine.

Management strategies

Effective early communication of the potential additional risks of AEDs in pregnancy is key, as many teratogenic effects occur in the first trimester. Options include:

- withdrawal of AEDs prior to conception. This may mean that pregnancy is delayed for a few years, so that AEDs are stopped safely;
- continuation of AEDs during pregnancy;
- stop AEDs in the first trimester, and restart them in the second;
- as a general rule, aim for monotherapy at the lowest doses possible, and try to avoid valproate.

If a preconception review was not possible, an in-depth discussion is required to consider whether to continue AEDs in pregnancy. If the decision is to stop treatment, AEDs should be tapered slowly to avoid rebound seizures.

If AEDs are taken during pregnancy, then:

- take a drug plasma level before or during early pregnancy to establish the effective dose for seizure control in that patient;
- plasma levels can then be monitored and doses adjusted throughout pregnancy to ensure continuing therapeutic plasma levels; this particularly applies to lamotrigine and levetiracetam, and, to a lesser extent, carbamazepine, phenytoin, and phenobarbital whose levels can change dramatically during pregnancy (see individual AEDs);
- monthly plasma levels are recommended with lamotrigine in high risk cases.

Harmful effects of AEDs during pregnancy can be minimized by:
1. folic acid (5mg/day) while patients are trying to conceive and during the first trimester to reduce the risk of neural tube defects;
2. specific screening regimes for fetal abnormalities;
3. neonatal vitamin K injections if the AEDs are enzyme-inducing. This will help prevent haemorrhagic disease of the newborn.

Contraception

Many of the commonly used AEDs (see Table 3.2) increase the metabolism of the oral contraceptive pill, thereby increasing the risk of unplanned pregnancy. If enzyme-inducing AEDs are used, then hormonal methods of contraception are not reliable. Barrier methods and coil devices should be considered. If oral contraceptives are the only acceptable option, then use high-strength formulations. In addition, higher doses of the morning after pill may be required.

Plasma lamotrigine levels decrease significantly when combined oral contraceptives (COCs) are co-prescribed. This can lead to worsening of seizure control in patients already established on lamotrigine or cyclical toxicity during the 7-day off-period with COCs.

Table 3.2 The effects of AEDs on the contraceptive pill

No effect	Reduced plasma levels	Not known
Acetazolamide	Carbamazepine	Paraldehyde
Benzodiazepines	Eslicarbazepine acetate	Stiripentol
Ethosuximide	Felbamate	
Gabapentin	Fosphenytoin	
Lacosamide	Lamotrigine	
Levetiracetam	Oxcarbazepine	
Methsuximide	Perampanel	
Piracetam	Phenobarbital	
Pregabalin	Phenytoin	
Retigabine	Primidone	
Tiagabine	Rufinamide	
Valproate	Topiramate	
Vigabatrin		
Zonisamide		

How to withdraw antiepileptic drugs

Risks and benefits of stopping antiepileptic drugs

AEDs have side effects, drug interactions, and the potential for teratogenicity. When seizure control is achieved, discontinuing AEDs is attractive for many patients. However, stopping AEDs comes with significant risks. The commonest is relapse. Twenty-five per cent of patients attempting to withdraw will relapse within 1 year, and ~30% will relapse within 2 years. In patients who had been seizure-free for 2 years, 59% of those stopping treatment remained seizure-free 2 years later, compared to 78% of patients who remained on medication. Of those who relapse, ~8% will not regain seizure control, even if the original AEDs are reinstated. Other physical risks of withdrawal include injury and death if tonic–clonic seizures develop. Social risks include the impact that having a further seizure may have on their potential to drive, work, and have children.

Timing of antiepileptic drug withdrawal

This is a matter of much debate but little evidence. A meta-analysis in children showed that seizure recurrence was less likely if patients were seizure-free for 2 years prior to stopping AEDs. There are no effective trials in adults. Expert consensus is that AED withdrawal in adults is also safer after 2 seizure-free years. In patients who have had surgical treatment for epilepsy, expert consensus again suggests it is safer to withdraw gradually after 2 years of treatment, although often long-term monotherapy is required.

Procedure of antiepileptic drug withdrawal

AEDs should be tapered, rather than abruptly stopped, to avoid seizure recurrence and status epilepticus. There is little evidence as to exactly how fast these medications should be withdrawn. Advice is to reduce AEDs sequentially, the speed of which depends on:

1. patient factors, e.g. the epilepsy type or the nature and degree of drug side effects experienced by the individual patient;
2. medication factors, e.g. dose, half-life, and duration of treatment.

If seizures recur, 50% happen in the withdrawal period, and 25% in the subsequent year. In the UK, patients should avoid driving during drug withdrawal and for 6 months afterwards.

If seizures occur during drug reduction, then the AED needs to be returned to the last dosage which successfully controlled the condition. Often a short-term course of clobazam or phenytoin can be used to reduce the increased seizure tendency occurring immediately following a seizure.

Status epilepticus

Status epilepticus is a life-threatening neurological disorder. It is defined as: 'more than 30 minutes of continuous seizure activity, or two or more sequential seizures without full recovery of consciousness between seizures'. In clinical practice, a seizure lasting longer than 5min can be considered the point at which urgent treatment is required to prevent the onset of established status. The prognosis of status epilepticus varies, depending on the underlying cause and any co-morbidity. The mortality rate is 2% in the healthy adult. Hypoxia, stroke, drug toxicity, co-morbidity, central nervous system (CNS) infection, longer status, and delayed effective treatment of status can push the mortality rate as high as 30%.

Investigation of status epilepticus

Preliminary investigation of status needs to be aimed at identifying the most likely causes (see Table 3.3):

- full physical assessment;
- blood screen: glucose, full blood count (FBC), C-reactive protein (CRP), liver and renal function tests, blood gases, calcium, magnesium, coagulation studies, screen for alcohol and drugs of abuse, and, in patients with known epilepsy, AED levels;
- consider chest X-ray (CXR), neuroimaging, LP, and EEG.

Table 3.3 Aetiology of status epilepticus in adults

	Aetiology	Percentage
Patient with a diagnosis of epilepsy	Low plasma levels of AEDs (e.g. non-compliance/omission)	~30%
	Refractory epilepsy	6%
Individuals without a previous diagnosis of epilepsy	Alcohol- and drug-related	~25%
	CNS infection	8%
	Refractory epilepsy	6%
	Trauma	6%
	Neoplastic space-occupying lesion	6%
	Acute stroke	6%
	Metabolic causes	4%
	Hypoxia	4%
Miscellaneous		6%

Adapted from Epilepsia, 40(2), Delorenzo RJ et al, Comparison of status epilepticus with prolonged seizure episodes lasting from 10 to 29 minutes, pp. 164–9, Copyright (1999), with permission from John Wiley and Sons; Epilepsy Curr, 10(2), Bleck T, Less common aetiologies of status epilepticus, pp. 31–33, Copyright (2010), American Epilepsy Society, reproduced under the Creative Commons Attribution 3.0 Unported License.

Intensive monitoring of physical and neurological observations, biochemistry, and EEG is required if status is sustained. Metabolic compromise and hypoxia are common consequences of prolonged seizures; they may both lower the chances of seizure termination and increase the risk of neuronal cell death.

Management of status epilepticus

Early and aggressive treatment of status epilepticus is essential. Management of status epilepticus needs to address the following three aspects in parallel (see Fig. 3.2):

1. resuscitation and cardiorespiratory support;
2. identification of the underlying cause of the seizure;
3. AED therapy.

Early status epilepticus

A. Benzodiazepines: the drug selected depends on:
   1. local availability of AEDs;
   2. availability of IV access:

      In the absence of IV access, the options are buccal midazolam 10mg or rectal diazepam 10–20mg;
      If IV access is available, then the options are IV diazepam 5–10mg or lorazepam 4mg.

All of these AEDs can be repeated at 10min if the seizures are not settling. IV diazepam or lorazepam alone in early status will terminate 60–80% and 60–90% of seizures, respectively.

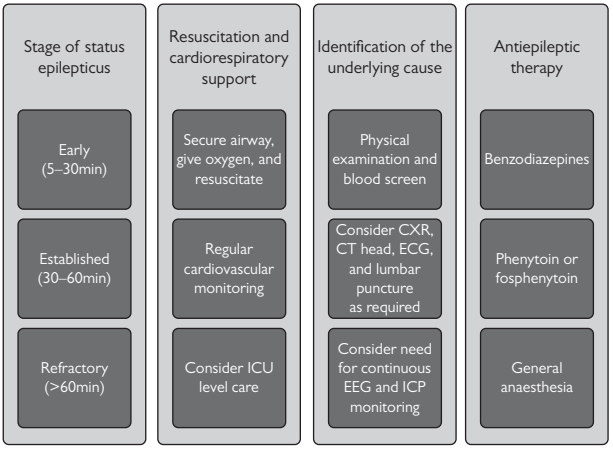

Fig. 3.2 Flow diagram summarizing the management of status epilepticus.

Evidence base

Good systematic reviews have shown IV lorazepam is associated with a significant reduction in the risk of seizure continuation and requirement for ventilatory support over diazepam (and over phenytoin). Diazepam may work slightly faster than lorazepam, because it is distributed more rapidly throughout the cerebrum, but its anticonvulsant effect is more short-lived (~20min, compared to 6h with lorazepam) because of rapid redistribution into fat and consequent fall in plasma levels.

B. Replace normal AEDs and correct obvious abnormalities. Omission of AEDs in patients with epilepsy can contribute to over 25% of prolonged seizures. Regular AEDs should be re-established as soon as possible. Loading doses of some drugs may be required, depending on how long the AEDs have been omitted. In addition, obvious precipitants should be corrected, e.g. alcohol withdrawal, electrolyte abnormalities, hypertension, and hypoglycaemia.

Established status epilepticus

- AEDs: if seizures fail to respond to benzodiazepines, then further AEDs are required.
- First line:
  - phenytoin: 15–20mg/kg by IV infusion at a rate of 50mg/min;
  - fosphenytoin: 15–20mg phenytoin equivalents/kg by IV infusion at a rate of 50–100mg phenytoin equivalents/min; or
  - phenobarbital: 10–15mg/kg by IV infusion at a rate of 100mg/min.
- Second line (these AEDs are used off-licence in the management of status; doses are derived from small RCTs, case study evidence, and expert consensus):
  - valproate: 20–30mg/kg by slow IV infusion at a rate 40–50mg/min. This can be followed by 1–3mg/kg/h maintenance infusion;
  - levetiracetam: 20–40mg/kg by IV infusion at 2–5mg/kg/min. This can be followed by 15mg/kg/12h maintenance infusion.

Regular blood pressure (BP) and ECG monitoring should be used in established status, both to monitor for complications of drug therapy and for complications of status itself.

Evidence base

There is sparse evidence for the management of established status.

- Phenytoin is the most widely used agent. It will terminate >50% of benzodiazepine-resistant seizures but carries significant risks of respiratory depression, hypotension, and sedation. Fosphenytoin is a phenytoin prodrug, which can be infused faster than phenytoin and, unlike phenytoin, is not associated with purple glove syndrome.
- Phenobarbital has comparable efficacy to phenytoin, terminating 60–70% of seizures unresponsive to benzodiazepines. It is often used second-line after phenytoin, due to perceived increased risks of respiratory depression and sedation. In fact, several randomized controlled studies have shown little difference in side effect profile when used in status.

- The evidence base for the use of valproate in status is limited. A systematic review of five RCTs carried out in China suggested that there was no significant difference in efficacy between valproate and phenytoin. It has the advantage of fewer sedative, cardiac, and respiratory side effects than phenytoin, but has several pharmacokinetic interactions of practical relevance, substantially increasing plasma levels of both phenobarbital and lamotrigine.
- Levetiracetam has a more favourable side effect profile than valproate and is under assessment for the treatment of refractory status. Evidence for its use in status is limited. A recent systematic review of one randomized study and ten observational studies reported ranges of efficacy from 44–94%.

Refractory status epilepticus

General anaesthesia (GA): it is estimated that ~30% of prolonged seizures progress to refractory status. At this point, a therapeutic coma is required to terminate seizure activity. The aim of GA is burst suppression on EEG. This is needed for at least 12h, before the GA can be slowly weaned over at least a further 12h. If seizures recur, the cycle is repeated again. The commonest agents used are propofol and midazolam. Thiopental and pentobarbital are barbiturate alternatives. Propofol should not be used for >5 days, as 'propofol infusion syndrome' can cause life-threatening liver failure and rhabdomyolysis.

- Doses:
  - propofol, in individuals >18 years: 2mg/kg bolus by IV injection at a rate of 20–40mg every 10s. Then give an infusion of 2–10mg/kg/h;
  - thiopental, in individuals >18 years: 75–125mg bolus (2.5%, 25mg/mL) (3–5mg/kg bolus in individuals <18 years), given as a slow IV injection. Then give up to 8mg/kg/h, as slow IV injection;
  - midazolam: 0.1–0.2mg/kg bolus by IV injection, followed by an infusion at 0.05–0.5mg/kg/h;
  - infusions are titrated to a level sufficient to provide burst suppression.

Evidence base

The evidence base is limited. A Cochrane review on the subject concluded that, for propofol and thiopental, there was insufficient evidence to suggest either drug was more effective. The only significant difference noted was a need to provide prolonged mechanical ventilation when thiopental was used.

Super-refractory status epilepticus

If propofol-, midazolam-, or barbiturate-induced coma fail to induce burst suppression, then status enters a stage which some experts have termed 'super-refractory status epilepticus'. This may occur in up to 15% of patients hospitalized with status. It is defined as status lasting longer than, or recurring after, 24h of anaesthetic-induced coma. The evidence base for treatment in this subgroup is minimal.

Alternative GA, such as lidocaine, ketamine, etomidate, or clomethiazole, hypothermia, corticosteroids, immunotherapy, the ketogenic diet, and neurosurgery are all potential options.

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Chapter 4

Cerebrovascular disease

Introduction

The World Health Organization (WHO) defines stroke as a syndrome characterized by 'rapidly developing clinical signs of focal (or, rarely, global, e.g. coma) disturbance of cerebral function, with symptoms lasting 24hs or longer, or leading to death, with no apparent cause other than of presumed vascular origin'. The key factors here are the sudden onset of a focal neurological syndrome (e.g. hemiparesis, dysphasia, visual field loss, etc.); non-focal syndromes (like loss of consciousness) are only rarely due to stroke. In modern practice, clinicians are unable to wait 24h to diagnose acute stroke, as strategies aimed at improving perfusion of the ischaemic penumbra need to be implemented as soon as possible following the onset of symptoms ('*Time is brain*').

Despite dramatic improvements in the treatment of acute stroke and in secondary stroke prevention over the last decade, mortality remains as high as 20% at 1 month. Moreover, up to 25% of survivors remain dependent for all their daily functions at 1 year. This makes stroke both the second commonest cause of death worldwide (after ischaemic heart disease) and the leading cause of neurological disability in the Western world.

Classification

Stroke can be classified as ischaemic (~85% of all strokes) or haemorrhagic (mainly intracerebral and subarachnoid; ~15%). Intracerebral haemorrhage (ICH) may be traumatic or non-traumatic (spontaneous). Spontaneous ICH can be further subdivided into primary or secondary—the former mainly arising from small-vessel pathology, e.g. hypertensive arteriopathy and cerebral amyloid angiopathy (CAA), and the latter arising from a variety of predominantly structural abnormalities, including arteriovenous malformations and tumours.

Ischaemic stroke

Ischaemic stroke is characterized by acute onset of a neurological deficit, resulting from cessation of blood flow to a focal area of the brain. For the most part, the area of the brain affected corresponds to the vascular territory of an occluded artery (see Table 4.1). The commonest mechanisms of ischaemic stroke are thromboembolic, cardioembolic, and small-vessel occlusion (see Fig. 4.1).

1. Thromboemboli primarily arise from atherosclerotic lesions, most commonly in the larger arteries of the neck (carotid or vertebrobasilar system artery disease) or within the medium-sized arteries of the brain (especially the middle cerebral artery, MCA). They may also occur following dissection of the carotid or vertebral arteries.
2. Cardioembolic strokes arise from embolization of cardiac thrombi, most commonly in the context of atrial fibrillation (AF) or ischaemic heart disease. Bacterial endocarditis, prosthetic heart valves, and atrial myxomas are other possible sources of emboli.
3. Small-vessel occlusion (i.e. lacunar strokes) are secondary to intrinsic pathology of small cerebral perforating end-arteries which supply the subcortical structures (basal ganglia, thalamus, internal capsule, and brainstem), and not the cerebral cortex. *In situ* disease of the small vessels, including microatheroma and lipohyalinosis, most commonly occurs as a consequence of hypertensive arteriopathy. A history of hypertension is present in ~80% of these patients, although this may be an overestimate, as hypertension is sometimes required in the definition of the stroke type.

Table 4.1 Expected neurological deficits following ischaemia of different cerebral artery vascular territories

Artery	Deficit of stroke
Anterior cerebral artery	Leg > arm and face (motor and sensory loss) Behavioural change (abulia)
Middle cerebral artery	Face, arm > leg (motor and sensory loss) Speech (left), neglect, homonymous hemianopia
Posterior cerebral artery	Homonymous hemianopia, cortical blindness if bilateral (rare)

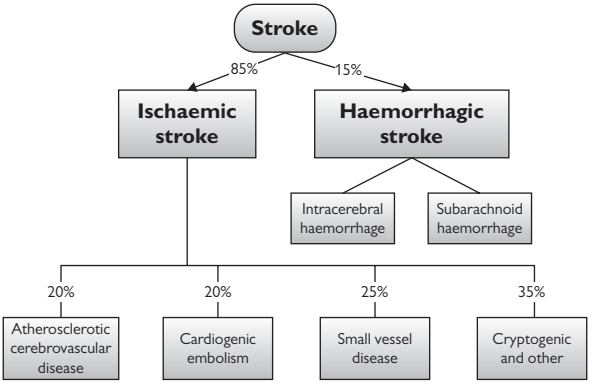

Fig. 4.1 Causes of stroke.

The most important risk factors for ischaemic stroke are age and hypertension, but smoking, diabetes, hyperlipidaemia, AF, coronary artery disease, family history of stroke, and personal history of previous stroke and transient ischaemic attack (TIA) are also important. In younger patients, oral contraceptive use, hypercoagulable states, vasoconstrictive drug use, craniocervical arterial dissection, polycythaemia, and sickle-cell disease should be considered.

Pathophysiology

Acute arterial occlusion to an area of the brain results in a spectrum of ischaemic damage to brain tissue, which depends on the size of the occluded vessel, the duration of occlusion, and the degree of collateral blood supply to areas of the brain within the territory of the occluded vessel. The area of affected brain comprises two distinct zones: the ischaemic core and ischaemic penumbra. The core is a region of the brain with such low blood supply that cell death occurs within minutes of the ischaemic insult. The penumbra is a variably sized area where blood supply from collateral vessels, or from the partially occluded affected vessel, is sufficient to maintain cellular survival for up to a few hours. Cells within the penumbra are deprived of oxygen and other elements essential for cellular metabolism, and hence lose many of the cellular protective mechanisms to further insults. Therefore, this area is very vulnerable to necrotic cell death from small changes in oxygen level, BP, blood glucose levels, etc.

The focus of early treatment is to facilitate recanalization (e.g. with fibrinolytics or endovascular clot removal devices) and to optimize the physiology of cells within the ischaemic penumbra by regulating important physiological parameters and rapidly treating complications, such as infection and seizures, which place an added metabolic strain on cerebral neurons.

Haemorrhagic stroke

Intracranial haemorrhage referes to any bleeding within the skull, including the subdural, extradural, subarachnoid, and intracerebral compartments. Conventionally the term 'haemorrhagic stroke' refers to non-traumatic intracerebral haemorrhage (ICH) (within the brain substance), or sometimes both intracerbral and subarchnoid haemorrhage. The commonest cause, accounting for about 80% of all of spontaneous (non-traumatic) ICH, is small-vessel disease, secondary to hypertension, and/or amyloid angiopathy. ICH accounts for ~10–15% of all strokes in developed countries and carries a 30-day mortality of 40–50%, most deaths occurring within the first 2 days. The clinical presentation depends upon the location and size of the haemorrhage and whether there is extension into the ventricles, secondary vasospasm, and/or hydrocephalus. Subarachnoid haemorrhage (SAH) is discussed in more detail in Subarachnoid haemorrhage, pp. 63–4.

Management of acute stroke: overview

The emphasis of early management is resuscitation and supportive measures, combined with rapid neuro-imaging to differentiate ischaemic from haemorrhagic stroke and allow decisions to be made regarding thrombolysis and other hyperacute interventions. Thus:

1. ensure a patent airway to avoid aspiration and hypoxia;
2. arrange urgent neuro-imaging to rule out haemorrhagic stroke. Computed tomography (CT) is usually the first-line imaging study because of its speed, availability, and ability to detect blood. MRI is much more sensitive to cerebral ischaemia in the hyperacute phase but, in many countries, is not yet as readily available;
3. monitor blood glucose, aiming for levels between 4 and 11mmol/L (insulin sliding scales can be used, if necessary). Occasionally, hypoglycaemia can mimic acute stroke.

If haemorrhagic stroke is excluded:

1. thrombolytic therapy is administered if the patient is seen within 4.5h of symptom onset and there are no contraindications;
2. antiplatelet therapy (aspirin 300mg) as soon as possible if outside of the thrombolytic window, or in 24–48h if thrombolysis has been given;
3. BP is monitored, and hypertension treated only if:
   - systolic persistently >220, diastolic>110, or mean arterial BP >130mmHg;
   - hypertensive encephalopathy, acute myocardial infarction (MI), aortic dissection, or severe heart failure is present;
   - the patient is to receive thrombolytic therapy, prior to which and during which BP should be maintained below 185/110mmHg.

If haemorrhagic stroke is identified:

1. the effects of anticoagulant agents should be urgently reversed and any other coagulopathy corrected, if possible;
2. if systolic BP >150, institute BP-lowering therapy, aiming for a target of 140mmHg systolic as soon as possible (ideally within 1h), unless there is a clear contraindication or other reason for caution.

All patients should be admitted to a dedicated stroke unit (or neurosurgical unit if surgical intervention is required).

Management of blood pressure in acute stroke

BP is a dynamic parameter in the early phases of acute stroke. There is limited evidence to help guide how tightly BP should be regulated. Early trials suggested that acute reduction in BP was associated with poorer outcomes. Subsequent randomized trials (*CATIS, SCAST, COSSACS*) have unfortunately failed to help establish a consistent approach to treatment for ischaemic stroke. There is some evidence that continuing existing antihypertensive therapy (when it can be safely and practically given) is probably safe in acute ischaemic stroke (*COSSACS* trial). Data from the INTERACT-2 trial suggest that lowering blood pressure in patients within the first 6 hours of acute ICH (to below 140mm systolic within 1 hour) improves functional

outcomes, and does not increase mortality or nonfatal adverse events. The optimum target for BP in both ischaemic and haemorrhagic stroke remains uncertain. General principles of best care are listed below.

1. BP management should be performed in a controlled manner and if required hyperacutely (within the first 24–48h) is best achieved with easily titrated IV agents.
2. When hypotension is present (systolic BP <120mmHg or BP significantly lower than premorbid state), the patient should be nursed supine, and administration of IV fluids considered to improve cerebral perfusion. Vasopressors may be considered if hypotension is severe and cannot be corrected by other means.
3. Candidates for thrombolysis who are hypertensive (systolic BP >185/110mmHg) should be given labetalol as an IV bolus of 10–20mg over 10min. If BP remains elevated, boluses can be repeated or a labetalol infusion given at 2–8mg/min. Alternative second-line agents include glyceryl trinitrate (GTN) and nicardipine.
4. BP should be maintained below 185/110mmHg throughout thrombolysis. After thrombolysis, BP should be recorded every 15min for 2h, then every 30min for 6h, and subsequently every hour for 16h.
5. In patients with ischaemic stroke not undergoing thrombolysis, there is little evidence to support treatment of hypertension. High BP often spontaneously resolves within the first 24h. The American Stroke Association recommends only treating elevated BP in the first 24h if there is malignant hypertension (as defined by BP which is so high that it has caused end-organ damage, e.g. stroke, MI, or renal impairment) or a co-morbidity that requires urgent BP-lowering therapy.

Ultimately, a clinician has to weigh up a patient's baseline BP, the type of stroke (see further text), whether or not a patient has been thrombolysed and hence is at a higher risk of bleeding, and the degree of extracranial (carotid or vertebrobasilar) artery stenosis (if known) and hence the potential increased risk of cerebral hypoperfusion with sudden drops in BP, among other factors.

The effects of variations in BP differ between stroke subtypes.

1. The penumbra of tissue following an ischaemic stroke has limited cerebral perfusion and hence theoretically may not tolerate acute drops in systemic BP; however, if the BP is too high, the chance of a haemorrhagic conversion may be increased.
2. In haemorrhagic stroke, elevated BP is associated with haematoma expansion, which can be reduced by intensive early treatment.

Ischaemic stroke and transient ischaemic attack

Management of acute ischaemic stroke

Acute treatment

1. If ischaemic stroke is identified within 4.5h of symptom onset (3h in the USA), and there are no contraindications, then thrombolysis—alteplase 0.9mg/kg over 1h, can be administered.
2. If ischaemic stroke is identified outside of the thrombolysis window, then antiplatelet therapy should be initiated as soon as possible. Antiplatelets should be held for 24–48h post-thrombolysis attempt.

Antiplatelet therapy

- First line: 300mg aspirin (acetylsalicylic acid, ASA) daily for 2 weeks (USA dosing: 325mg).
- Second line: 300mg single dose, then 75mg clopidogrel for 2 weeks.
- Longer-term antiplatelet therapy: see Secondary prevention following ischaemic stroke or transient ischaemic attack, pp. 57–60.

Evidence base

Antiplatelet therapy

Aspirin monotherapy is the only antiplatelet treatment proven to be effective in very early stroke. The International Stroke Trial (IST) included nearly 20 000 patients with suspected acute ischaemic stroke; 300mg aspirin given within 48h reduced the 14-day recurrence of ischaemic stroke (2.8% vs 3.9%) and of non-fatal stroke or death (11.3% vs 12.4%), compared with placebo. The Chinese Acute Stroke Trial (CAST) included 21 100 patients randomized to 160mg of aspirin daily or placebo within 48h of acute ischaemic stroke, and showed that aspirin reduced total mortality at 1 month by 14% (absolute percentages 3.3% with aspirin vs 3.9% with placebo).

A recent meta-analysis of early dual antiplatelet therapy (aspirin and clopidogrel, aspirin and dipyridamole, aspirin and cilostazol) vs monotherapy (aspirin, clopidogrel, or dipyridamole) for acute ischaemic stroke or TIA included over 9000 participants, including the CHANCE, EARLY, and FASTER trials (enrolled within 24h), as well as those from other trials where the antiplatelet agent was given within 72h of onset. Dual antiplatelet therapy was associated with a 31% reduction in recurrent stroke (relative risk (RR) 0.69, 95% CI 0.60–0.80) and composite vascular events and death (RR 0.71, 95% CI 0.63–0.81), and a non-significant increase in major bleeding (RR 1.35, 95% CI 0.70–2.59). The interpretation of these findings is complicated by great heterogeneity within the populations, variations in other drug therapy and follow-up, and low adverse event rates.

Thus, there may be added benefit of dual antiplatelet therapy (e.g. 21 days of aspirin and clopidogrel in the *CHANCE* trial) after a TIA or minor ischaemic stroke, but larger studies are required to confirm this, particularly in populations outside Asia.

Thrombolysis

For patients treated within 3h, the initial trials demonstrated an increase in good functional outcome and a non-significant trend towards a 4% decrease in mortality with alteplase. A recently published meta-analysis of all the current RCTs of thrombolytics in acute ischaemic stroke (12 trials, 7012 patients) demonstrated that thrombolysis given within 6h of stroke significantly increased the probability (4.2%) of being both alive and independent (Modified Rankin Scale (MRS) 0–2) at final follow-up (OR 1.17, 95% CI 1.06–1.29; $p = 0.001$). The analysis confirmed that the greatest benefit in neurological outcome was demonstrated in patients treated within 0–3h (MRS 0–2, 365/896 [40·7%] vs 280/883 [31·7%], OR 1.53, 95% CI 1.26–1.86; $p < 0.0001$). Mortality within 7 days was increased by 2.5% in those who were thrombolysed (primarily accounted for by intracranial haemorrhage). However, by final follow-up, this excess mortality was no longer significant. The benefit of thrombolysis was also seen in those >80 years.

Other agents trialled in the acute treatment of ischaemic stroke

1. Clinical trials of streptokinase were halted prematurely because of unacceptably high rates of haemorrhage. Currently, the only fibrinolytic agent licensed for thrombolysis is alteplase.
2. Abciximab is a monoclonal antibody, which binds to glycoprotein IIb/IIIa receptors, thereby inhibiting platelet aggregation. Despite early results showing positive outcomes when used in ischaemic stroke, AbESSTT-II (Abciximab in Emergency Treatment of Stroke Trial), a large phase 3 multicentre, randomized, double-blind, placebo-controlled trial, showed no difference in outcomes at 3 months between placebo- and abciximab-treated patients. However, within the first 5 days, there was a markedly increased number of symptomatic or fatal ICH in the abciximab-treated group (5.5% vs 0.5% with placebo), and the trial was terminated early. Abciximab is thus not recommended for use in acute ischaemic stroke.

Surgical interventions

Decompressive hemicraniectomy should be strongly considered in the ~10% of ischaemic stroke patients who have a 'malignant' MCA syndrome (characterized by rapid deterioration in neurological function due to the rapid rise in ICP with cerebral oedema, following a large infarct of the MCA territory). Surgery should be performed within 48h of symptom onset for best results. The randomized trial evidence for benefit is most convincing in individuals <60 years, but some older patients may also benefit (DESTINY 2 trial).

Transient ischaemic attacks

TIAs are neurological deficits of ischaemic origin that typically last from a few minutes to usually no more than 30min. A TIA may be indistinguishable from an ischaemic stroke at presentation, and patients need to be managed as per acute ischaemic stroke guidelines if presenting within 24h of onset with persistent weakness. TIA is pathophysiologically identical to ischaemic stroke, but the symptoms are transient because reperfusion occurs, either from adequate collateral circulation or as a result of emboli fragmentation.

Table 4.2 ABCD2 score

Age ≥60	1 point
BP ≥140/90	1 point
Clinical features:	
Unilateral weakness	2 points
Speech disturbance without weakness	1 point
Duration of symptoms:	
≥1h	2 points
10–59min	1 point
Diabetes	1 point

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A focused history is essential, as TIA mimics, such as migraine aura or focal epilepsy, are commonly mistakenly diagnosed as TIA and subsequently inappropriately managed. In cases of diagnostic uncertainty, MRI with diffusion-weighted imaging (DWI) and blood sensitive sequences is recommended.

The ABCD2 score (see Table 4.2) is used to estimate the risk of stroke after a TIA and guides the urgency of further investigations, although it does not take into account key prognostic factors, e.g. carotid stenosis, AF, recurrent attacks, or MRI-detectable brain ischaemia, which also need to be considered.

The risk of stroke within 48h is:

- 1% in low-risk patients with a score of 1–3;
- 4.1% in moderate-risk patients with a score of 4–5;
- 8.1% in high-risk patients with a score of 6–7.

In the UK, NICE recommends that a patient scoring ≥4 should be assessed by a specialist and have neuro-imaging within 24h, and that all patients with scores less than this should be seen and imaged if required within 7 days. In modern stroke practice, all patients with suspected TIA or minor stroke should be assessed urgently by a stroke specialist. Diffusion-weighted MRI should be used, except where contraindicated, in which case CT is undertaken. Recent evidence suggests that blood-sensitive MRI sequences should also be performed to exclude TIA syndromes related to intracranial bleeding.

Treatment

Antiplatelet therapy after TIA is similar to that for ischaemic stroke. Secondary prevention of modifiable risk factors needs to be implemented as soon as possible.

Acute management

- First line: aspirin 300mg daily for 2 weeks (USA: ASA 325mg).
- Second line: clopidogrel 300mg daily for 2 weeks.
- Third line: dipyridamole 200mg bd.

Evidence base

The *EXPRESS* study, although non-randomized, provided evidence that there was a significant benefit in treating patients with TIA or minor stroke swiftly. This study took a cohort of patients with TIA/minor strokes who had not required admission to hospital but were felt to be managed safely in a rapid access clinic or primary care clinic setting. The primary outcome was the risk of stroke within 90 days of seeking medical attention. Early initiation of treatment was shown to be associated with an 80% reduction in the risk of early recurrent stroke (adjusted hazard ratio 0.2, 95% CI 0.08–0.49; $p = 0.0001$).

Secondary prevention following ischaemic stroke or transient ischaemic attack

Patients diagnosed with stroke and TIA have a high risk of recurrent ischaemic events. In fact, ~25% of all strokes are recurrent events, and the risk of stroke in a patient who has had a TIA is about 10% per year. In addition, these patients have a higher risk of cardiovascular, renovascular, and peripheral vascular disease. Thus, appropriate secondary prevention is crucial. Ongoing treatment with antiplatelets is recommended, and additional factors must be considered and appropriately monitored as follows.

Antiplatelet therapy

- Longer-term secondary prevention:
  - first line: clopidogrel 75mg once daily (od);
  - second line: aspirin 75mg od and dipyridamole modified-release (MR) 200mg bd;
  - third line: aspirin 75mg od.

Evidence base

- ASA ± dipyridamole MR (200mg bd) can be used in those who are intolerant of clopidogrel and, like clopidogrel monotherapy, is more efficacious than ASA alone. The use of antiplatelet therapy reduces the RR of stroke, MI, and death by ~22%; this is equivalent to 25 fewer strokes per 1000 patients treated for a mean of 29 months. While aspirin monotherapy was traditionally used in the management of ischaemic stroke, the use of the newer antiplatelet drug regimens, i.e. monotherapy with clopidogrel or dipyridamole, in addition to aspirin, has shown to result in a reduction of one vascular event per year for every 100 patients treated, when compared to aspirin monotherapy.
- Dual antiplatelet therapy: two randomized trials have assessed the utility of longer-term dual antiplatelet therapy with aspirin and clopidogrel in the treatment of ischaemic stroke. The evidence is currently inconclusive. In the *MATCH* trial comparing aspirin and clopidogrel vs clopidogrel alone, and the *CHARISMA* trial comparing aspirin and

clopidogrel vs aspirin alone, no significant change in ischaemic vascular events were identified, yet there was a significant increase in the rate of life-threatening bleeds. Long-term dual antiplatelet therapy is generally therefore not indicated for routine ischaemic stroke secondary prevention. (although the case may be different for ischaemic stroke secondary to intracranial stenosis)

Vascular risk factors

1. *Lifestyle*: advice should be given regarding lifestyle, including smoking cessation, dietary advice, weight control, avoidance of excess alcohol, and optimization of physical activity.
2. *BP*: a definitive target BP after stroke has not been established; however, an average reduction of 10/5mmHg is associated with improved outcomes in clinical trials. The most effective antihypertensive agent to prevent stroke is not known. However, benefit has been demonstrated with angiotensin-converting enzyme (ACE) inhibitors, thiazide-like diuretics, and calcium channel blockers. Recent data emphasize the importance of consistent optimized BP control to reduce variability, particularly to prevent ICH; there is some evidence that calcium channel blockers may reduce BP variability more than other agents.
3. *Lipid levels*: in both the UK and USA, statin therapy is recommended for any patient who has had a stroke or TIA, unless any contraindications to their use exist (see Statins, pp. 342–7). In the UK, guidelines recommend that statins should be started 48h after the onset of symptoms but should not be stopped in those who are already on treatment for ischaemic stroke, while, in the USA, statins may be started following symptom onset.

Evidence base

- A meta-analysis of >90 000 patients taking part in previous statin trials demonstrated that the larger the reduction in low-density lipoprotein (LDL) cholesterol, the lower the risk of consequent ischaemic stroke. The efficacy of statin therapy in the secondary prevention of ischaemic stroke is well documented. It has also been demonstrated that statin therapy should be initiated as swiftly as possible following ischaemic stroke (see Statins, pp. 342–7). The *HPS* study involved 3280 adults with cerebrovascular disease who had previous non-disabling ischaemic stroke, TIA, and/or a history of carotid endarterectomy or angioplasty. Patients were allocated to either 40mg simvastatin or placebo and monitored over a 5-year treatment period. Retrospective subset analysis of these patients with symptomatic ischaemic cerebrovascular disease demonstrated a 20% reduction in major vascular events (HR 0.80, 95% CI 0.71–0.92) and a 19% (non-significant) reduction in further ischaemic stroke. Similarly, on-treatment analysis of 4162 patients involved in the *SPARCL* trial revealed an 18% reduction of further ischaemic stroke in those treated with 80mg atorvastatin daily, when compared to placebo (HR 0.82, 95% CI 0.69–0.98; $p = 0.03$).

4. *Diabetic control*: strict glycaemic control in diabetics reduces microvascular, and macrovascular, complications. The goal for HbA1c should be ≤7% (IFCC 53.0). In the IRIS study, patients with recent ischaemic stroke or TIA without diabetes who had insulin resistance along with a recent history of ischemic stroke or TIA, the risk of stroke or myocardial infarction was lower among patients who received pioglitazone than among those who received placebo.

Atrial fibrillation

AF is the commonest cause of cardio-embolic stroke. Any patient with AF who has had a stroke or TIA, in the absence of any clear contraindications, automatically qualifies for oral anticoagulation, according to the CHADS2 and CHADS2 VASc scores. These are the most commonly used risk stratification scores used to assess the risk of cardio-embolic stroke in patients with AF.

The most commonly used anticoagulant is warfarin, but the novel oral anticoagulants apixiban, dabigatran, and rivaroxaban have emerged as attractive alternatives to warfarin for stroke prevention in AF. They have shown similar efficacy for stroke prevention and generally lower rates of ICH, compared to warfarin. Another benefit is the apparent lack of requirement for regular monitoring and dose adjustment, but more real-world observational follow-up data outside trials are required to definitively establish longer-term safety and efficacy. The lack of an effective antidote remains a concern.

Warfarin anticoagulation for long-term secondary prevention in patients with AF can be safely commenced 2 weeks post-ischaemic stroke or TIA, as demonstrated in the European Atrial Fibrillation Trial. Some clinicians begin warfarin earlier, taking into account the extent of cerebral infarction, e.g. starting immediately after TIA or after a few days for small infarcts. Randomized trials are needed to clarify the optimum timing of anticoagulation in acute ischaemic stroke. The commonest time point for haemorrhagic transformation post-ischaemic stroke is in the first 1–4 days after symptom onset, but later haemorrhage from 7–14 days (and occasionally beyond) can occur. Cerebral microbleeds may be associated with an increased hazard of intracranial haemorrhage in patients anticoagulated after cardioembolic stroke due to AF; this is being investigated in the CROMIS-2 observational study, and current data does not allow a firm recommendation to be made about anticoagulant use in those patients with cerebral microbleeds.

Extracranial carotid or vertebral artery dissection

In the setting of extracranial vertebral or carotid artery dissection causing ischaemic stroke, oral anticoagulation is often considered; however, evidence originates from non-randomized trials and has failed to consistently demonstrate any benefit over antiplatelet therapy. A 2010 Cochrane review was unable to find any RCTs comparing the use of antiplatelets with anticoagulants in the management of carotid artery dissection. Analysis of over 30 observational studies suggested there was no significant difference in the odds of ischaemic stroke or death between the two treatments, although there may be a non-significant trend towards reduced death or disability in favour of oral anticoagulants (OR 1.77; $p = 0.06$). More intra- and

extracranial haemorrhages occurred in the anticoagulated group. A recent trial (CADISS) found no difference in efficacy of antiplatelet and anticoagulant drugs in preventing stroke and death in patients with symptomatic carotid and vertebral artery dissection; however, there were very few outcome events. Further trials are needed before firm guidance can be given. However, currently, many stroke experts recommend anticoagulation if there is clear evidence of ongoing embolism in association with extracranial dissection. Anticoagulation should be avoided in the much rarer setting of intracranial arterial dissection due to the risk of catastrophic SAH.

Symptomatic carotid artery stenosis

Symptomatic carotid artery stenosis is responsible for a subgroup of ischaemic strokes. It is important to clinically separate this group of patients, as they may benefit from carotid revascularization procedures, i.e. carotid endarterectomy or stenting procedures. These techniques aim to prevent further thromboembolic strokes arising from symptomatic carotid arteries. Endarterectomy is more commonly used and current practice is to consider all patients with symptomatic carotid stenosis >50% for revascularisation or best medical treatment, following multidiscipilinary team discussion. Specific plaque chracteristics, e.g. ulceration (on noninvasive angiography) or intraplaque haemorrhage (on dedicated MRI) may help to predict high early stroke risk in carotid stenosis.

For patients with ischaemic stroke or TIA due to symptomatic intracranial stenosis, dual antiplatelet therapy (aspirin and clopidogrel) is recommended following the SAMMPRIS trial, which showed the superiority of aggressive of medical treatment compared with endovascular treatment (stenting). Short-term dual antiplatelet therapy (e.g. 3–4 weeks) is also often recommended for patients with symptomatic extracranial arterial stenosis (e.g. carotid or vertebrobasilar stenosis).

Intracerebral haemorrhage

ICH is associated with a significant risk of further ICH of up to about 10% per year. The risk may be much higher for ICH due to CAA than for hypertensive ICH.

Management of acute intracerebral haemorrhage

The focus of pharmacological treatment of ICH is prevention of haematoma expansion. Thus, any coagulopathy needs to be normalized, and extremes of BP should be controlled as quickly as possible:

1. Haemostatic agents: in patients taking anticoagulants, rapid administration of an antidote is required. In the context of warfarin, this is usually IV vitamin K, with prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP), depending on local availability. PCC is superior to FFP in normalising the INR and smaller haematoma expansion in vitamin K antagonist related ICH, but was not powered to demonstrate improved outcomes. Protamine sulfate should be given to reverse heparin. The novel oral anticoagulants apixaban, dabigatran, and rivaroxaban have no specific antidote currently, although agents are in development. Treatment with prothrombin complex and close liaison with a haematologist are recommended for these patients. Platelet transfusion has recently been shown to be unhelpful (and likely harmful) in acute ICH related to prior antiplatelet use (PATCH trial).
2. Antihypertensives: the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) trial using IV nicardipine and the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trials (INTERACT-1 and 2) using a mixture of antihypertensives have both demonstrated that systolic BP reduction to 140mm Hg is well tolerated and associated with attenuation of haematoma expansion. The ATACH-2 trial suggested that more intensive treatment in acute ICH to achieve a target systolic blood pressure of 110 to 139mm Hg did not result in a lower rate of death or disability than reduction to a target of 140 to 179mm Hg. Thus, rapid BP lowering beyond a target of 140mm Hg systolic is not recommended in acute ICH.

Therapies under investigation

1. Thrombolysis for intraventricular haemorrhage: a pilot study investigating the use of intraventricular urokinase in the management of intraventricular haemorrhage found a trend to lower mortality and faster resolution of intraventricular haemorrhage. Further larger studies are needed.
2. Recombinant factor VIIa (rFVIIa): preliminary studies suggested that treatment with rFVIIa was safe and effective for ICH. However, results from a multicentre, double-blind, phase 3 clinical trial were disappointing. Compared with placebo, treatment with rFVIIa was associated with a significant reduction in haematoma expansion. However, this was not associated with improvement in the primary outcome measures of death or severe disability at 90 days.

3. Tranexamic acid (TA): the CRASH 2 study, a nested RCT investigating the impact of TA on intracranial bleeding in the context of traumatic brain injury, was unable to reliably demonstrate significant benefits with use of TA. An ongoing phase 3 RCT (TICH-2 study) is aiming to establish if TA is effective and safe in the management of hyperacute primary ICH. The dose given in trials for this indication is 1g IV given over 10min, followed by an IV infusion of 1g given over 8h.

Surgical interventions

Surgical decompression of large intracranial haemorrhages may be indicated for patients with symptomatic hydrocephalus, significant neurological disability, and/or evidence of elevated ICP. Non-invasive surgical approaches (MISTIE trials) in ICH show promise in improving functional outcome in acute ICH, but larger definitive trials are needed.

Secondary prevention of intracerebral haemorrhage

The main target for secondary prevention is reduction of BP; the PROGRESS trial showed that the benefit of BP reduction after ICH exceeded the benefit seen in ischaemic stroke. The optimum target is unknown, but a target of less than 140mm Hg is usually recommended; observational data suggest that sustained BP control (smoothing out high peaks) may be especially important in preventing ICH. Other modifiable risk factors linked to ICH recurrence include diabetes, excessive alcohol consumption, and cigarette smoking.

Anticoagulants, antiplatelets, and statins following intracerebral haemorrhage

Unless there is a clear indication, antithrombotics (antiplatelets and anticoagulants) should be avoided after ICH, particularly in the presence of CAA. Statins may also increase recurrent ICH risk, particularly in CAA where some experts recommend avoidance in the absence of a clear indication. The RESTART trial is investigating whether stopping or continuing antiplatelet drugs is preferable in patients with ICH and a clear indication for antiplatelet use (e.g. vaso-occlusive disease).

When haemorrhagic stroke has occurred in association with oral anticoagulant or antiplatelet agent use, a risk–benefit analysis needs to be undertaken, weighing up the possible chances of a re-bleed with the chance of a recurrent thrombotic event. There is no clear evidence in this area. The ongoing *APACHE-AF* trial is investigating if and when to restart an oral anticoagulant or antiplatelet agents following an intracranial bleed and will hopefully inform management in this challenging area. In patients with ICH with a high risk of future ischaemic stroke due to AF, left atrial appendage occlusion, which appears to be as safe and effective as oral anticoagulation with warfarin, may be reasonably considered.

The use of statins after ICH remains controversial. In the SPARCL trial, patients with ICH at baseline had a higher risk of future ICH when treated with atorvastatin, compared with placebo. Moreover, some studies have found an inverse relationship between total and LDL-cholesterol and the risk of ICH. However, subsequent studies and meta-analyses have not confirmed definitively whether statins increase the risk of future ICH. It is therefore reasonable to balance the benefits and possible risks of statin therapy in individual patients, according to an assessment of the risks of vaso-occlusive events and future recurrent ICH.

Subarachnoid haemorrhage

SAH accounts for ~5% of strokes and has an incidence rate of 6–9 per 100,000 patient years. It typically occurs in patients <60 years of age. The commonest causes of SAH are aneurysmal rupture (particularly saccular berry aneurysms, 85%), arteriovenous malformations, trauma, clotting disorders/anticoagulants, tumours, and vasculitis. It classically presents with a sudden and severe ('thunderclap') headache, worst at the occiput and associated with neck stiffness, presumably secondary to blood in the subarachnoid space. Dizziness, nausea, and vomiting (which may be transient or protracted) can also be experienced. Impaired level of consciousness and focal neurological signs may occur, particularly if there is associated ICH. Seizures occur in ~7% of patients.

In patients with a typical history, an urgent high-resolution non-contrast CT head scan within 12h of symptom onset has a sensitivity of 98–100%. Sensitivity falls to 93% at 24h, further declining to 57–85% at 6 days. If there is a highly suggestive history and no evidence of haemorrhage on an acute CT scan, then an LP is recommended to confirm or refute a diagnosis of SAH by looking for the presence of xanthochromia at ~12h after symptom onset. This is present in 100% of patients up to 14 days, and in 70% up to 21 days, after SAH onset. MRI fluid-attenuated inversion recovery (FLAIR) sequences may be helpful in patients with normal CT scans and equivocal cerebrospinal fluid (CSF) results, although routine use in the acute scenario is often precluded by lack of availability and the lengthy duration of the scan.

Management

The acute management of SAH involves resuscitation and early implementation of interventions designed to prevent common complications, namely further bleeds, vasospasm, and hydrocephalus. The following measures must be taken to stabilize the patient.

1. *Resuscitation and neuro-observations*: advanced life support techniques, particularly fluid resuscitation, to maintain cerebral perfusion, and close neurological monitoring are important.
2. *BP control*: systolic BP should be maintained between 90 and 140mmHg prior to aneurysm treatment. Hypotension should be corrected with colloid or inotropes to maintain adequate cerebral perfusion and prevent vasospasm. Hypertension should be corrected with antihypertensives that can be titrated rapidly. If there are no contraindications, IV labetalol is the agent of choice.
3. *Prevention of vasospasm*: patients should be adequately hydrated, electrolyte abnormalities corrected, and nimodipine 60mg 4-hourly (or as close to this as tolerated) initiated. Nimodipine, at this dose, has been demonstrated to reduce the chance of cerebral infarction, following SAH, from 33% to 22%. This correlates with improved clinical outcomes.

4. *Management of raised ICP* (see Raised intracranial pressure, p. 195 in Chapter 13, Neuro-oncology): patients with signs of raised ICP or brain herniation will require intubation and hyperventilation. The use of excessive hyperventilation, as well as agents, such as mannitol, which may cause dehydration and hypotension, should be avoided in order to prevent worsening vasospasm.
5. *Seizure prophylaxis*: this is currently an area of significant uncertainty. Some studies have demonstrated no connection between functional outcome and seizures, and retrospective investigations have demonstrated adverse effects from AEDs. Nonetheless, seizures may potentially increase the risk of re-rupture of an unsecured lesion. At present, if seizure prophylaxis is deemed necessary, the treatment of choice is IV phenytoin. There is lack of experience with other AEDs in this setting. Long-term prophylactic anticonvulsant therapy is not routinely recommended.
6. *Analgesia and antiemetics*: these are important to minimize distress and ensure adequate hydration and the maintenance of a steady BP.
7. *Definitive neuroradiological or neurosurgical treatment*: following confirmation of the diagnosis and appropriate stabilization of the patient, early discussion with a regional neurosurgical centre is essential to identify scope for neuroradiological or neurosurgical intervention.
   - *Antifibrinolytics*: antifibrinolytics significantly reduce rates of re-bleeding, but this benefit is offset by an increased risk of secondary cerebral ischaemia and thrombosis, so they are not used for SAH in clinical practice.

Cerebral venous sinus thrombosis

Thrombosis in the cerebral veins is an uncommon and under-recognized form of stroke. It accounts for 0.5–1% of all strokes and occurs more commonly in young individuals. Risk factors include dehydration, ear or sinus infections, long-haul air travel, trauma, surgery, oral contraceptives, inflammatory bowel disease, pregnancy, and prothrombotic haematological conditions

Headache is common and usually diffuse in nature, progressing in severity over days to weeks, although occasionally there is a thunderclap presentation, causing diagnostic confusion with SAH. Focal neurological deficits are usually due to focal brain injury from infarction or haemorrhage. Appropriate investigations include CT venography (to detect sinus filling defects), T2*-weighted MRI (to visualize the thrombus directly and detect areas of haemorrhage or infarction), and magnetic resonance (MR) venography. Digital subtraction angiography can help to clarify cases of diagnostic uncertainty, despite non-invasive testing.

Treatment

In the acute setting, IV unfractionated heparin or treatment-dose low-molecular-weight heparin (LMWH) is used, even if there is haemorrhage on brain imaging. Limited data suggest that LMWH is more effective than unfractionated heparin and at least as safe for the treatment of cerebral venous sinus thrombosis. Anticoagulation has been shown to be safe and effective in small randomized trials. There is no evidence to support the use of antiplatelet agents in cerebral venous sinus thrombosis.

In those patients who deteriorate despite anticoagulant therapy, endovascular thrombolysis (e.g. with direct administration of recombinant tissue plasminogen activator (rt-PA) into the occluded sinus through an IV catheter) or mechanical disruption of the thrombus have been tried, with some reported success. Where the ICP is raised due to mass effect from venous infarction, decompressive craniectomy may be lifesaving, but trials are lacking. Long-term management is with oral anticoagulants. Treatment duration is typically 3–12 months, depending on the presence and nature of risk factors for venous thromboembolism (VTE). In cases with an underlying thrombophilia tendency, treatment may be needed lifelong.

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Chapter 5

Neuropathic pain

Introduction

Neuropathic pain can be defined as '*pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system*'. This is distinct from nociceptive pain, which can be described as '*pain resulting from a noxious stimulus*'. Neuropathic pain syndromes comprise a heterogeneous group of disorders, for which there are still no accurate data with regards prevalence. Various studies have estimated that anywhere between 1–8% of Western populations may be affected. In terms of specific disease aetiologies, roughly 16–26% of people with diabetes will suffer from painful diabetic neuropathy, and 8–19% of patients with varicella-zoster rash will develop post-herpetic neuralgia.

Classification

The following classification system is based on the clinical grouping of conditions that occurs in most neuropathic pain trials and is outlined by the EFNS guidelines on management of neuropathic pain:

- painful neuropathies (mono-/polyneuropathies):
  - polyneuropathies—hereditary, toxin-/drug-related, immune-mediated, metabolic;
  - diabetic mononeuropathy, polyneuropathy, amyotrophy;
  - post-herpetic neuralgia;
  - infective/post-infective, e.g. HIV neuropathy;
  - carcinoma-related, e.g. paraneoplastic, myeloma;
  - phantom pain;
  - nerve trauma.
- chronic radiculopathy;
- central pain syndrome;
- trigeminal neuralgia;
- complex regional pain syndromes, e.g. fibromyalgia.

Treatment of neuropathic pain

Initiation: when starting pharmacotherapy for neuropathic pain, consideration must be given to the aetiology and severity of the pain, including impact on activities of daily living and sleep, as well as patient factors such as co-morbidities and age.

Review: patients should be reviewed soon after initiation of treatment and regularly thereafter to assess efficacy and tolerability and to monitor dose titration. A specialist pain service may be useful if pain is severe and poorly responsive to initial management and if psychological factors are prominent.

Withdrawal: medication cessation should be undertaken gradually and closely monitored for any aggravation of pain or withdrawal symptoms.

Evidence-based recommendations for the treatment of individual neuropathic pain syndromes

This advice is based on the 2010 EFNS guidelines for the treatment of neuropathic pain.

Painful polyneuropathy

This is an aetiologically diverse group of conditions, excluding post-herpetic neuralgia, diabetic neuropathy, and HIV neuropathy. Painful polyneuropathy can be caused by drugs, toxins, gammopathies, and inflammatory, paraneoplastic, and metabolic conditions. A number of inherited conditions may also cause painful neuropathies, including hereditary sensory and autonomic neuropathies, familial amyloid polyneuropathies, and mitochondrial disorders.

Treatment

- First line: gabapentin, pregabalin, or tricyclic antidepressants (TCAs).
- Second line: tramadol.
- Third line: strong opioids.

Evidence base

A meta-analysis of several small RCTs demonstrated the efficacy of TCAs (NNT 2.1, 95% CI 1.8–2.6) in painful polyneuropathy. Despite good evidence of efficacy of duloxetine, gabapentin, and pregabalin in diabetic painful polyneuropathy, there are no substantial trial data for their use in painful polyneuropathy of other aetiologies.

Diabetic neuropathy

This is the most prevalent sensory neuropathy in Europe and the USA, usually presenting as a chronic distal sensory small-fibre, or mixed small- and large-fibre, polyneuropathy. Good glycaemic control is an important preventative measure and may halt progression of the condition.

Treatment

- First line: serotonin and noradrenaline reuptake inhibitors (SNRIs).
- Second line: gabapentin, pregabalin, or TCAs.

Evidence base

A number of robust RCTs demonstrate efficacy of duloxetine for pain relief in diabetic neuropathy. These data have been consolidated in a

meta-analysis demonstrating an NNT of 5 (95% CI 4–7) for a 50% reduction in pain over 12 weeks. Gabapentin, TCAs, and pregabalin have all been shown to be effective in meta-analyses with an NNT for 50% pain reduction of 5.8 (95% CI 4.3–9), 1.3 (95% CI 1.2–1.5), and 5.0 (4.0–6.6), respectively.

Post-herpetic neuralgia

Post-herpetic neuralgia is a common form of neuropathic pain that can follow infection by varicella-zoster. It is commoner in the elderly and occurs in ~20% of people post-herpes zoster infections. The pain, which affects the dermatomal level(s) involved by the zoster rash, usually starts after the herpetic vesicles have crusted over, and typically lasts for over 3 months.

Treatment

- First line: gabapentin, pregabalin, TCAs, or topical lidocaine (in the elderly).
- Second line: strong opioids or topical capsaicin.

Evidence base

There is good evidence from multiple large RCTs and meta-analyses for the efficacy of gabapentin, pregabalin, and TCAs in the treatment of post-herpetic neuralgia. The NNT for 50% pain reduction was 7.5 (95% CI 5.2–14) for gabapentin 1800mg daily, 4.0 (95% CI 3.1–5.5) for pregabalin 600mg daily, and 2.2 (95% CI 1.6–3.1) for global improvement in pain scores with TCAs.

Two RCTs have confirmed that strong opioids are effective (1.9-fold reduction in pain intensity; $p < 0.001$). There are data from two placebo-controlled RCTs demonstrating marginal efficacy for lidocaine patches in post-herpetic neuralgia; however, they are expensive, and thus EFNS and NICE recommend their use only for patients who cannot tolerate/use oral medications, particularly the elderly. Finally, there is strong evidence from a meta-analysis for the efficacy of high-strength, but not low-strength, topical capsaicin (NNT = 8.8, 95% CI 5.3–26).

HIV neuropathy

HIV commonly causes a painful distal symmetrical axonal polyneuropathy. The neuropathological mechanism is unknown. Furthermore, dideoxynucleoside reverse transcriptase inhibitor drugs used extensively in HIV treatment can also cause an acute toxic neuropathy.

Treatment

- First line: topical capsaicin or lamotrigine.
- Second line: cannabinoids.

Evidence base

Most conventional pharmacological treatments for neuropathic pain do not effectively alleviate symptoms associated with HIV neuropathy. Moderate evidence for efficacy has been demonstrated from small individual placebo-controlled RCTs for lamotrigine (57% received pain relief vs 23% with placebo; $p = 0.004$), smoked cannabis (34% received pain relief vs 17% with placebo; $p = 0.03$), and the high-dose capsaicin patch (22.8% received pain relief vs 10.7% with placebo; $p = 0.0026$).

Cancer-related neuropathic pain

Cancer-related neuropathic pain can be due to remote or local effects of the disease, or secondary to chemotherapy. Cancer pain is usually of mixed aetiology, rather than purely neuropathic, and so strong opioids are often used. In addition to conventional therapies for neuropathic pain, opportunities to target pain through oncological therapies can also be considered.

Treatment

- First line: gabapentin.
- Second line: TCAs or tramadol.

Evidence base

There is a lack of good-quality clinical trials in neuropathic pain associated with cancer. There is some evidence showing efficacy for gabapentin in one RCT (0.8 point reduction in pain intensity, compared to placebo; $p = 0.025$), and tramadol (improvement in pain scores; $p < 0.001$). The only RCT of TCAs in cancer-associated neuropathic pain found no benefit from adding amitriptyline to morphine.

Phantom pain

Phantom pain is due to cortical sensory perception of an amputated body part. Its reported incidence varies widely between studies, due to differing definitions of phantom pain. At least 80% of amputees will experience abnormal sensations in the amputated body part at some point. When phantom pain does manifest, it occurs within days of the operation/injury in 75% of cases.

Evidence base

There are conflicting recommendations for the treatment of phantom pain. The oral analgesic with the best efficacy in trials is morphine (53% pain relief, compared to 19% with placebo; $p < 0.0001$; NNT for 50% pain relief = 5.6). Gabapentin has shown discrepant results in RCTs. There is evidence for the preoperative use of IV morphine and IV ketamine and for the use of epidural anaesthesia with morphine and bupivacaine.

Traumatic neuropathic pain

Nerve damage can occur following trauma, with 3% of trauma victims sustaining significant peripheral nerve injury and a large proportion of these suffering from long-term neuropathic pain. Trauma may also be iatrogenic, particularly in oral and maxillofacial surgery. An estimated 0.5–2% of maxillofacial procedures will result in the development of long-term neuropathic pain.

Treatment

- First line: amitriptyline.
- Second line: botulinum toxin and gabapentin.

Evidence base

There is minimal evidence for pharmacotherapy in traumatic neuropathic pain. Gabapentin achieved only a few secondary outcome measures in a multicentre trial. In individual smaller trials, amitriptyline reduced pain

by 50% in 8/15 patients, and botulinum toxin injections improved global pain relief in 40%, compared to 14% with placebo (p <0.05; NNT for 50% pain relief = 3.03). Currently, botulinum toxin injections are not universally recognized as a treatment for neuropathic pain and are not licensed for this indication.

Chronic radiculopathy and plexopathy

Damage to a nerve root or roots can result in pain, as well as weakness and numbness in the root territory. Lumbar and brachial plexopathies can also cause pain. Causes include trauma, mechanical impingement, diabetes, and infections such as HIV and Lyme disease.

Evidence base

No agent has shown consistent pain relief in RCTs. TCAs and strong opioids show the best results.

Central neuropathic pain

Central neuropathic pain is due to disruption of the pain pathways within the CNS. The commonest causes are stroke, MS, and spinal cord injury.

Treatment

- First line: amitriptyline, gabapentin, or pregabalin.
- Second line: tramadol.
- Third line: strong opioids.

NB. Cannabinoids may alleviate central pain in patients with MS.

Evidence base

Several systematic reviews suggest a moderate effect of both pregabalin 600mg (NNT = 5.6, 95% CI 3.5–14 for 50% pain reduction) and gabapentin (improvement in pain scores ranging from 0.873 to 3.362 on a 10-point scale; p <0.05, in four RCTs) for pain following spinal cord injury. There is weak evidence from an RCT for amitriptyline post-spinal cord injury (reduction of pain scores by 2.46 on a 10-point scale, compared to diphenhydramine; p = 0.035), but not post-stroke. Individual RCTs provide some evidence for efficacy of strong opioids (15% pain reduction with high-dose, compared to low-dose, μ-opioid agonist; p = 0.02) and tramadol (7/23 patients rated improvement in pain, compared to 1/12 with placebo; p = 0.04). One RCT indicated that Sativex®, an oromucosal cannabinoid spray, may help to relieve neuropathic pain symptoms in MS (reduction in pain score by 0.79 on a 10-point scale, compared to placebo; p = 0.038).

Trigeminal neuralgia

Trigeminal neuralgia presents with brief, intense periods of electric shock-like pain distributed along the territory of the trigeminal nerve. Classical trigeminal neuralgia is idiopathic or secondary to vascular compression of the trigeminal nerve at the cerebellopontine angle, and symptomatic trigeminal neuralgia occurs as a result of structural lesions such as cerebellopontine angle masses or MS.

Treatment

- First line: carbamazepine or oxcarbazepine.
- Second line: lamotrigine or phenytoin.

Evidence base

Carbamazepine has been used to treat trigeminal neuralgia since the 1960s. As such, much of the evidence is anecdotal or from very old and small trials. A recent meta-analysis combined two trials of 98 patients and demonstrated that carbamazepine provided better analgesia than placebo, with an NNT of 2 (95% CI 1–2). Three RCTs support the use of oxcarbazepine in the place of carbamazepine on the basis of comparable efficacy (88% of patients achieve a reduction in attacks by >50%) and a superior side effect profile. A recent Cochrane review concluded that there is insufficient evidence to recommend lamotrigine for trigeminal neuralgia, despite one RCT demonstrating a beneficial effect. Finally, microvascular surgical decompression may be of benefit for drug-resistant classical trigeminal neuralgia.

Combination pharmacotherapy in neuropathic pain

A recent Cochrane review assessed currently available data for combination therapy in neuropathic pain and concluded that there was insufficient evidence to advise any specific combination if monotherapy fails. Both NICE guidelines and the International Association for the Study of Pain (IASP) guidelines concur.

On the basis of past and current clinical practice, the following drug combinations may be beneficial:

1. TCAs in combination with pregabalin;
2. Duloxetine in combination with pregabalin;
3. Tramadol as an adjunct in any neuropathic pain syndrome;
4. Gabapentin, in combination with a TCA or a strong opioid, may be useful in some patients (EFNS guidelines).

Other drugs studied in neuropathic pain

In addition to the drugs discussed in detail in this section, many other drugs have been studied for their potential use in treating neuropathic pain. These drugs are not included in the above treatment recommendations, as either there is insufficient evidence currently to prove their efficacy, results are conflicting, or they appear to be of no benefit.

1. *Alternative antidepressants*: although the recent NICE guidelines for neuropathic pain still include five selective serotonin reuptake inhibitors (SSRIs) (citalopram, escitalopram, fluoxetine, paroxetine, sertraline) for the treatment of neuropathic pain, there is very little evidence for their efficacy. Most trials have been too small and/or show conflicting results. The only meta-analysis to assess SSRIs in neuropathic pain concluded that better-quality data are required, before a conclusion can be made regarding their efficacy. The antidepressants phenelzine and bupropion have shown some benefits in small trials, but St John's Wort and trazodone have appeared ineffective in studies to date. None of these drugs are currently recommended for the treatment of neuropathic pain by any international body, and they are not licensed for this indication in the UK or USA.
2. *Alternative antiepileptics*: a recent meta-analysis assessed the efficacy of AEDs in neuropathic pain and fibromyalgia. Good second-tier evidence was found for gabapentin and pregabalin, but no significant evidence of efficacy was identified for clonazepam, phenytoin, and sodium valproate. Lacosamide, lamotrigine, and topiramate were deemed either ineffective or at best minimally effective.
3. *Other drugs*: other drugs trialled in neuropathic pain include dextromethorphan, memantine, and *N*-methyl-*D*-aspartate (NMDA) receptor antagonists. These drugs have shown conflicting results in small trials for the treatment of phantom pain. In addition, memantine has been shown to be ineffective for pain relief in diabetic, post-herpetic, and HIV neuropathy, and dextromethorphan has shown no effect in post-herpetic neuralgia.

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Chapter 6

Inflammatory disorders of the central nervous system

Introduction

Autoimmune inflammatory mechanisms are increasingly implicated in the pathogenesis of a wide range of neurological diseases. Immunomodulatory treatment for MS is a rapidly evolving field. Several new agents have been licensed since 2010, and more are expected in the next few years.

General principles of immunotherapy

In general terms, immunotherapy for neurological autoimmune diseases varies, depending on the disease being treated, its severity, the mechanism of the aberrant immune response, patient co-morbidities, response to prior treatments, and current guidelines for best treatment. However, the overall therapeutic approach is similar and involves initial control of inflammation, followed by maintenance of remission.

Induction of remission

Corticosteroids are very effective at rapidly reducing inflammation and are widely used, given initially at high doses to control disease, then tapered to reduce the risk of side effects. Conditions in which circulating autoantibodies are pathogenic generally respond to treatments targeting B cells or interfering with antibody–antigen interactions such as IV immunoglobulin (IVIg) and plasma exchange (PLEX).

Maintenance immunotherapy

Low-dose corticosteroid maintenance may be required, or may be substituted or supplemented by immunosuppressants with a slower onset of action but more acceptable long-term side effects. Steroid-sparing immunosuppressants commonly used in neurology include azathioprine, methotrexate, mycophenolate, and cyclophosphamide. Antibody-mediated diseases are generally treated with agents which preferentially target B cells, such as cyclophosphamide or rituximab, in preference to agents with more general immunosuppressant activity. Biological therapies, such as anti-tumour necrosis factor (TNF) agents, natalizumab, and rituximab, which target specific components of the immune system, are beginning to replace traditional immunotherapy but are expensive.

Multiple sclerosis

MS is by far the most prevalent inflammatory disorder of the CNS, affecting 120 per 10000 in Europe and the USA, typically young adults. It is characterized by widespread patchy, inflammatory demyelination throughout the CNS. Most patients (90%) experience a relapsing–remitting course from onset (RRMS), with discrete episodes of neurological dysfunction (relapses) interspersed with periods of clinical disease inactivity (remissions). Relapses are the result of episodes of enhanced inflammatory demyelination within the CNS, but subclinical inflammation is present, even when symptoms are absent. MS has a predilection for the optic nerves, brainstem, cerebellum, and spinal cord, producing characteristic clinical syndromes, including optic neuritis, ataxia, transverse myelitis (TM), and brainstem disease, with diverse signs such as the pathognomonic internuclear ophthalmoplegia.

Aetiology

The cause of MS remains unknown. Both genetically determined susceptibility and an environmental trigger, probably viral, are thought to be required. Epstein–Barr virus (EBV) infection has been strongly implicated in MS pathogenesis, and vitamin D deficiency is known to be a significant risk factor for the development of MS. To date, over 150 MS susceptibility genes have been identified. Most are involved with the major histocompatibility complex (MHC), and many are vitamin D-responsive elements.

Pathology

Immunopathology is driven by autoreactive T cells, which initiate complex inflammatory mechanisms involving cellular and humoral processes and ultimately cause demyelination and axonal loss. Although traditionally considered a white matter disease, primarily involving myelin and oligodendrocytes, it has become increasingly clear that the cortical grey matter is also targeted and that axon loss occurs acutely, as well as later, in the course of MS. The latter is an important determinant of disability and cognitive dysfunction, as the disease progresses.

Clinical course

Most patients with RRMS eventually go on to develop secondary progressive MS (SPMS), manifest as a slow, but relentless, accumulation of disability, independent of relapses. Progressive axon loss, rather than inflammatory demyelination, is responsible for clinical progression. Brain volume loss, measured with MRI, correlates closely with clinical disability in the progressive phase. Low-level inflammation, mediated by innate immune cells within the CNS, may also contribute to disease progression. A small proportion (10%) of patients have gradually progressive disease from onset, termed primary progressive MS (PPMS). It is not clear whether SPMS and PPMS involve identical pathological processes, but, once progression is established, clinical deterioration proceeds at the same rate in both conditions, suggesting a common pathology.

Management

The pharmacological treatment of MS can be divided into drugs that reduce the duration of an acute relapse, those that act to maintain remission from relapses, and thus limit the accumulation of disability ('disease-modifying therapy', DMT), and symptomatic therapies designed to ameliorate the symptoms produced by CNS lesions.

Treatment of relapses

- First line: PO methylprednisolone 500mg daily for 5 days of IV methylprednisolone 1g daily for 3 days.
- Proton pump inhibitor for the duration of the steroid course.

Short courses of high-dose corticosteroids shorten relapse duration but have no impact on the degree of recovery from a relapse or upon subsequent disease course. Regimes vary throughout Europe and the USA, but the authors recommend the above approach. There is no strong evidence of benefit to support the use of a PO prednisolone taper.

Evidence base

Of six RCTs investigating the use of corticosteroids in acute relapses of MS, five demonstrated that the percentage of patients whose symptoms remained unchanged or deteriorated was much higher with placebo than with corticosteroids. All of four small trials comparing PO with IV steroids found that PO steroids were non-inferior to IV steroids in terms of efficacy and side effects.

Disease-modifying therapy

- Moderately-effective
  - Interferon beta
  - Glatiramer acetate
  - Teriflunomide
- More effective
  - Dimethyl fumarate
  - Fingolimod (licensed for 2nd line use only in the UK)
- Highly effective
  - Nataluzimab (for highly active disease)
  - Alemtuzumab
  - Mitoxantrone

Disease modification in MS is a rapidly developing field. Several drugs have emerged over recent years, and there is a healthy pipeline of new agents in development. Modification of the early course of RRMS is achieved primarily by reducing the frequency and severity of relapses, thus limiting relapse-associated accumulation of disability. As a result, all currently available DMTs are licensed for RRMS, rather than the progressive forms. It is not clear whether DMTs may prevent or delay the onset of progressive MS. To date, they have not been shown to influence the rate of clinical disability progression in established progressive MS (SPMS or PPMS). However, it has recently become apparent that some DMTs may reduce the rate at which brain atrophy occurs. Neuroprotection is a focus of current research, and several agents are undergoing evaluation in clinical trials. Repair strategies, including stem cell therapies,

potentially able to reverse established demyelination and axon loss or to promote intrinsic repair and remyelination, are also at early stages of development.

Efficacy of DMTs is measured in terms of impact on relapse frequency (annualized relapse rate (ARR), time to next relapse, risk of relapse) and disability accumulation (time to increase in disability as measured by the Expanded Disability Status Scale (EDSS), sustained for 3 or 6 months), and in terms of the effect on MRI indicators of disease activity—accumulation of new and enlarging T2 lesions, gadolinium-enhancing lesions, total lesion load, and increasingly on MRI indicators of axon loss or progression (T1 lesion volume, total brain volume). The concept of disease-free status or 'no evidence of disease activity' (NEDA), long used in rheumatology, has recently been adopted in MS and is calculated using a combination of these parameters.

Moderately effective therapies

Injectable DMTs IFN-β and glatiramer acetate have a modest effect on clinical and MRI indices of MS activity in RRMS and excellent long-term safety. In established RRMS, these drugs reduce relapse rate by ~30%, with a similar effect on relapse-associated accumulation of disability. There is increasingly compelling evidence that treatment initiated early in the course of the disease, after the first clinical event (clinically isolated syndrome), may be even more beneficial, and most clinicians would offer first-line DMTs after a single clinical event of at least moderate severity, particularly if MRI showed a high lesion load and a lot of inflammatory activity suggesting the patient is likely to develop active disease subsequently.

Oral alternatives to IFN-β and glatiramer have recently become available. The first to be licensed fingolimod has greater efficacy, but a risk of first-dose bradycardia requiring observation and cardiac monitoring for 6h. In the UK, NICE approval has been granted for second-line therapy only, but it is used first-line elsewhere. Teriflunomide has similar efficacy to IFN-β and glatiramer acetate, and a favourable side effect profile. Dimethyl fumarate shows superior efficacy to the first-line injectable therapies, resulting in 44–53% relapse rate reduction, and is well tolerated.

Highly effective therapies

Alemtuzumab is a highly effective therapy, reducing relapse rate by 70–80%. It is given in two IV courses, 1 year apart, and has been approved as first-line therapy in highly active disease.

Relapsing MS that remains highly active, despite appropriate first-line therapy, requires escalation of treatment with more potent agents. People with rapidly evolving severe disease may be treated with natalizumab or alemtuzumab (or fingolimod in Europe and the USA) without prior IFN-β or glatiramer treatment. Natalizumab reduces the relapse rate by 70% or more, but its use is limited by the rare, but potentially fatal, side effect of progressive multifocal leukoencephalopathy (PML). Alemtuzumab has been approved in Europe, but not yet in the USA. Mitoxantrone, although also very effective in terms of relapse reduction, is now rarely used because of serious side effects of cardiotoxicity and leukaemia.

Vitamin D and multiple sclerosis

There is an inverse relationship between sun exposure, ultraviolet radiation exposure, or serum vitamin D levels and the risk or prevalence of MS. Accumulating data suggest that low serum vitamin D levels increase the risk of developing MS and adversely affect MS disease course. Most clinicians currently recommend that all people with MS take vitamin D3 (colecalciferol) supplements 1000–2000iu daily (or 20000iu every 2 weeks), aiming for serum 25-hydroxy vitamin D levels comfortably within the sufficient range (>30ng/mL or >75nmol/L).

Fulminant/malignant multiple sclerosis

Occasionally, MS presents with an aggressive, fulminant course with rapid accumulation of new lesions and neurological deficits, despite high-dose IV methylprednisolone. There is no strong evidence base to guide management in these unusual circumstances, but PLEX, natalizumab, and mitoxantrone have been reported to be of benefit. Guidelines from the AAN state that plasmapheresis should be considered for the adjunctive treatment of exacerbations in patients with relapsing forms of MS. Early natalizumab treatment is recommended by the AAN and Association of British Neurologists (ABN) for aggressive-onset relapsing MS.

Treatment of symptoms

Common MS-related symptoms include spasticity, urinary dysfunction (detrusor overactivity and/or detrusor–sphincter dyssynergia), constipation, erectile dysfunction, fatigue, pain (dysaesthesia, neuralgia, and musculoskeletal pain secondary to gait abnormalities), depression, paroxysmal symptoms, tremor, and oscillopsia. Agents used to treat these symptoms are discussed in detail in the relevant chapters. A symptomatic treatment unique to MS, and therefore covered in this chapter, is fampridine, a slow-release formulation of 3,4-DAP, which has been shown to significantly improve walking speed in a proportion of people with MS.

Other CNS inflammatory disorders

Neuromyelitis optica

Neuromyelitis optica (NMO), previously known as Devic's disease, is a rare relapsing demyelinating disorder, now known to be distinct from MS. It typically presents with a combination of optic neuritis, often bilateral and sequential, and longitudinally extensive (>3 vertebral segments) myelitis. There is a high early morbidity and mortality from severely disabling attacks, often leading to permanent disability if not treated promptly. In a minority, the disease is monophasic. There is no progressive phase of the sort seen in MS, but relapses are common. MRI brain scans may be normal or show non-specific white matter changes not typical of MS. Circulating antibodies against aquaporin 4 (AQP4), a water channel abundant in the CNS, are pathogenic. Limited forms (NMO spectrum disorders) include recurrent myelitis, recurrent optic neuritis, or atypical presentations associated with AQP4 antibodies.

Treatment

Acute

- First line: corticosteroids—IV methylprednisolone 1g daily for 3–5 days, followed by PO prednisolone 0.75–1mg/kg daily, tapering by 5mg every month to a maintenance dose of 20mg od or 40mg alternate days.
- Second line: PLEX for resistant relapses (those with no significant improvement 10 days after steroid initiation).

Maintenance

- First line: prednisolone plus azathioprine, or rituximab monotherapy.
- Second line: methotrexate 15–25mg once weekly, mycophenolate 1g bd, cyclophosphamide, mitoxantrone, regular IVIg, or PLEX.

Remission can usually be achieved promptly with corticosteroids as above, but resistant relapses should be treated early with PLEX. Most patients can be kept relapse-free with long-term immunosuppression. EFNS guidelines recommend first-line therapy as either rituximab or a combination of azathioprine and prednisolone. Azathioprine should be started early and increased to a target dose of 2.5–3mg/kg daily (bd dose). Rituximab is given by IV infusion at a dose of 1000mg on days 1 and 14, repeated 6-monthly. Prednisolone can be reduced further to 10mg daily, or even discontinued in stable disease.

Evidence base

There are no RCTs of immunotherapy in NMO. An open-label study of rituximab showed a dramatic reduction in relapse rate at 1 year, so many experts recommend rituximab as first-line therapy.

Site-restricted inflammatory diseases

Transverse myelitis

TM is a clinical syndrome with multiple potential causes. Infections precede approximately two-thirds of cases, and post-infectious autoimmune mechanisms are likely to be responsible for the majority, although direct infection can also play a role. TM also occurs in the setting of MS, NMO, and a variety of systemic autoimmune conditions.

Treatment

- First line: IV methylprednisolone 1g daily for 3–7 days.
- Second line: PLEX.
- Third line: cyclophosphamide.

Once infection has been ruled out, acute treatment is with high-dose corticosteroids. If response is suboptimal, PLEX should be given (1.5 plasma volumes in five treatments over 10 days), ideally within 2 weeks of onset, although its efficacy has been demonstrated if given within 2 months. Severe or treatment-resistant cases may rarely be treated with cyclophosphamide. Underlying conditions, such as MS and NMO, should be identified and treated, as appropriate.

Evidence base

There are no RCTs to support the use of methylprednisolone for TM, despite considerable positive clinical experience and several small observational studies confirming its benefit. The efficacy of PLEX has been demonstrated by RCTs in severe and steroid-unresponsive TM. Several small series support the use of cyclophosphamide in severe cases.

Optic neuritis

Treatment

- First line (if clinically indicated): IV methylprednisolone 1g daily for 3 days, or PO methylprednisolone 500mg daily for 5 days.

Treatment of typical forms of optic neuritis with high-dose corticosteroids shortens the period of acute visual dysfunction but does not affect the final visual outcome. However, the majority of cases do not require treatment, particularly in view of the small, but not insignificant, risk of avascular necrosis of the hip associated with high-dose steroid treatment. Any underlying predisposition to optic neuritis, such as MS or NMO, should be identified and treated, as indicated.

Evidence base

The Optic Neuritis Treatment Trial (ONTT), in alignment with several small studies, found that IV methylprednisolone resulted in faster recovery of visual function, compared with placebo. Controversially, results from the ONTT also suggested that IV methylprednisolone treatment reduced the subsequent risk of recurrent optic neuritis and conversion to MS, and that PO prednisolone treatment led to increased risk of a second episode. These findings have never been replicated, and the general consensus is that corticosteroid treatment for optic neuritis has no

impact on subsequent risk of developing MS or recurrent optic neuritis. In a Cochrane database, a meta-analysis of trials evaluating high-dose IV steroid treatment found no conclusive evidence of long-term benefit in terms of recovery to normal visual acuity, visual field, or contrast sensitivity with either IV or PO corticosteroids.

Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is an autoimmune demyelinating disease of the CNS that typically follows a febrile infection or a vaccination in children and young adults. There is usually acute or subacute onset of meningism, encephalopathy, and multifocal CNS deficits. Optic nerve involvement, when present, is typically bilateral. MRI shows scattered areas of demyelination restricted to the brain and spinal cord. It is usually monophasic, and spontaneous recovery generally begins within a few weeks, with complete resolution in 2–6 months. Controversy exists over the potential risk of subsequent development of MS or NMO. Acute haemorrhagic leukoencephalopathy is a rare form of severe fulminant ADEM, distinguished only by the presence of severe MRI changes, including haemorrhages, a more aggressive course, and poor outcome, despite intensive immunotherapy.

Treatment

- First line: IV methylprednisolone 20–30mg/kg/day (maximum 1g daily) for 3–5 days ± PO prednisolone taper over 3–6 weeks.
- Second line: IVIg 2g/kg over 2–5 days or PLEX.

Evidence base

There is a lack of evidence-based, prospective clinical trial data for the management of ADEM. Empirical antibacterial and antiviral treatment is indicated, until an infectious disease process is ruled out. Case series support the benefit of corticosteroids, as do a limited number of controlled clinical trials. Cases with limited response to steroids should be treated early with IVIg, which may be given as first-line treatment, instead of steroids, if infectious meningoencephalitis cannot be definitely excluded. PLEX should be given in severe or resistant cases. There is a lack of specific recommendations for the long-term management of severe refractory or recurrent/multiphasic ADEM, but rituximab, ciclosporin, and cyclophosphamide have been given, with some success.

Primary angiitis of the central nervous system

Primary angiitis of the CNS (PACNS) is a rare condition in which inflammation of small to medium arteries is restricted to the CNS. This should be distinguished from CNS vasculitis seen in association with a variety of systemic conditions. PACNS is often difficult to diagnose and is associated with significant morbidity and mortality. Clinical presentation is heterogeneous and may include headache, subacute encephalopathy, and strokes (arterial and venous). Distinction should be made between PACNS and the more benign posterior reversible vasoconstriction syndrome. Formal cerebral angiography may show typical appearances of vasculitis, but generally a brain biopsy is required to confirm the suspected diagnosis.

Treatment

- First line: corticosteroids (PO prednisolone 60mg/day; IV methylprednisolone 1g/day in severe cases) plus cyclophosphamide (monthly IV pulse of 1g or PO 150mg/day).
- Second line: rituximab.

There is no standardized treatment protocol to guide management. Corticosteroids, in combination with cyclophosphamide, are effective in most patients. Rituximab may be given in treatment-resistant cases. Switching to a safer immunosuppressant, such as azathioprine, methotrexate, or mycophenolate, may be considered after 6 months.

Evidence base

No RCT evidence exists for any form of treatment of PACNS, and management guidelines represent expert opinion, based primarily on trials investigating therapies for systemic vasculitides with severe organ involvement.

Autoimmune limbic encephalitis

Limbic encephalitis usually presents with a triad of confusion, memory loss, and seizures. Herpes simplex encephalitis is the commonest and most important cause. In recent years, antibodies directed against cell surface antigens have been detected in cases of non-infectious limbic encephalitis. Different clinical phenotypes are associated with certain autoantibodies as follows.

- *VGKC antibody encephalitis* is associated with antibodies to components of the VGKC complex, including LGI1 and CASPR2. Hyponatraemia is common, and there may be preceding faciobrachial dystonic seizures.
- *AMPAR antibody encephalitis* presents as a rapidly progressive encephalitis, often with acute psychosis. Thymoma, small cell lung cancer (SCLC), or breast cancer are present in 70% of cases.
- *$GABA_BR$ antibody encephalitis* is characterized by prominent temporal lobe seizures in the setting of a subacute encephalopathy. Half of cases are associated with SCLC.
- *GAD antibody encephalitis* typically affects younger people; seizures are prominent, and there may be associated stiff person and cerebellar syndromes. Progressive encephalomyelopathy with rigidity and myoclonus (PERM) is another very rare clinical manifestation of a GAD and/or glycine-mediated encephalopathy.
- *NMDAR antibody encephalitis* typically affects young women but is also seen in men. Subacute cognitive and behavioural change, psychosis, and seizures are followed by choreoathetosis and dysautonomia, then mutism and catatonia. Ovarian teratoma is present in up to 50% of cases.

Treatment

- First line: corticosteroids plus IVIg or PLEX.
- Second line: rituximab, cyclophosphamide, azathioprine.

Autoimmune limbic encephalitis generally responds to immunotherapy with high-dose corticosteroids, IVIg, or PLEX, and outcomes are improved with early and aggressive immunotherapy.

Response of VGKC antibody encephalitis to immunotherapy is good, and recurrence is rare. Associated faciobrachial dystonic seizures usually show an excellent response to corticosteroids.

NMDAR antibody encephalitis should be treated with early and intensive immunotherapy, as the natural history of the condition can be severe and prolonged, and at least 25% of untreated patients without tumours have relapsing disease. Removal of the ovarian tumour, when present, expedites recovery. Often additional immunotherapy is required, and rituximab and cyclophosphamide are used most frequently.

Evidence base

There are no RCTs of immunotherapy in autoimmune limbic encephalitis. Treatment is currently dictated by expert consensus and based on experience with other antibody-mediated neurological disorders.

Susac's syndrome

This is a rare autoimmune endotheliopathy which causes the clinical triad of encephalopathy, branch retinal artery thrombosis, and sensorineural hearing loss, most commonly in otherwise healthy women 20–40 years old. MRI shows typical corpus callosal microinfarctions but may be mistaken for MS.

Treatment

- First line: corticosteroids and azathioprine or cyclophosphamide.
- Second line: TNF antagonists.

Evidence base

Single case reports and anecdotal evidence support the efficacy of aggressive immunosuppression with corticosteroids and azathioprine or cyclophosphamide.

Multisystem diseases with central nervous system involvement

Sarcoidosis

Sarcoidosis is a multisystem granulomatous disease of unknown cause, which affects the nervous system in fewer than 10% of cases. Cranial neuropathies due to granulomatous basal meningitis, seizures, hydrocephalus, mass lesions, myelopathy, and hypothalamic and pituitary involvement with endocrinopathy can occur.

Treatment

- First line: prednisolone 0.5–1mg/kg (maximum 80mg) following IV methylprednisolone 1g daily for 3 days in severe disease, slowly tapering.
- Second line: methotrexate 10mg weekly or hydroxychloroquine 200mg daily.

Corticosteroids are usually effective, but high doses for prolonged periods are often required. As a rule, up to 20mg daily is required to maintain symptom freedom, but cautious reduction and withdrawal can be attempted (by 1mg every 2–4 weeks) if symptoms do not recur. If response to steroids is inadequate, methotrexate or hydroxychloroquine can be added. Cyclophosphamide, ciclosporin, chlorambucil, azathioprine, mycophenolate, or anti-TNF therapies may be given in refractory disease. Rarely, cranial irradiation and neurosurgery may be indicated for hydrocephalus or mass lesions.

Evidence base

There are no RCTs for neurosarcoidosis, and management is based on data from pulmonary sarcoidosis.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a relatively prevalent multisystem autoimmune disease, affecting ~1 in 1000 of the population. It is commoner in females, Afro-Caribbeans, and Asians. Diagnostic criteria published by the American College of Rheumatology require four of 11 features to be present at some time during the course of the illness: malar rash, discoid rash, photosensitivity, mouth ulcers, arthritis, serositis (pleurisy or pericarditis), renal involvement (casts or proteinuria), neurological disorder, haematological disorder (haemolytic anaemia, cytopenia), immunological disorder, and positive antinuclear antibodies (ANAs).

Neuropsychiatric involvement is present in up to 50% of cases and can include seizures, headache, chorea, psychiatric and cognitive disturbance, myelopathy (there is a link with NMO), and stroke. The predominant pathology is small-vessel vasculopathy and microinfarction, sometimes with macroscopic infarction from Libman–Sacks endocarditis or prothrombotic antibodies. True inflammatory vasculitis is rare. Circulating antibodies include ANA and others directed towards components of cell nuclei. Antiphospholipid antibodies, which target

β2-glycoprotein, and lupus anticoagulant are prothrombotic and contribute to arterial and venous thrombosis. Antiphospholipid syndrome (APLS) refers to the presence of these prothrombotic antibodies and can occur in association with SLE (or other rheumatological disorders) or in isolation (primary APLS).

Treatment

Non-stroke neurological involvement

Acute

- First line: cyclophosphamide (weekly IV pulse or daily PO for 9–12 weeks) plus IV methylprednisolone 1g/day for 3 days, followed by PO prednisolone 60mg/day, then taper.
- Second line: rituximab, IVIg.

Maintenance

- First line: prednisolone (10–20mg alternate days) plus mycophenolate, azathioprine, or methotrexate.
- Second line: rituximab.

Thrombotic complications in antiphospholipid syndrome with or without systemic lupus erythematosus

Acute

- First line: treatment-dose heparin or LMWH.

Secondary prevention of thrombotic events

- First line: aspirin 75mg.
- Second line: LMWH or warfarin.

Patients with prothrombotic antibodies, which are independent risk factors for stroke, and those with thromboembolic events are given aspirin, which is probably superior to warfarin in this setting. Aspirin is also recommended for primary prevention, although without much evidence base.

Serious (non-stroke) neurological complications of neurological lupus are treated with immunosuppressant therapy, as above. Prednisolone 60mg daily can be tapered by 10mg every week to 10mg daily for 9–12 weeks. Longer-term maintenance is with prednisolone 10–20mg and either mycophenolate, azathioprine, or methotrexate.

Evidence base

There are no large RCTs for neurological lupus. Treatment of patients with severe neurological involvement is based on one small randomized trial and experience of treating lupus nephritis. Systematic reviews show cyclophosphamide to be superior to pulsed methylprednisolone as a maintenance therapy. Small series and case reports suggest that IVIg may be of value. Biological agents are under evaluation. The beneficial effects of rituximab in severe refractory SLE have been reported in 24 case series. Two RCTs failed to achieve their primary endpoints, but both studies were widely acknowledged to have major design limitations.

Giant cell arteritis

Giant cell arteritis (GCA), or temporal arteritis, is a large-vessel vasculitis, affecting people over the age of 50 years and presenting with

headache, scalp tenderness, constitutional symptoms, polymyalgia rheumatica, visual disturbance, and occasionally jaw, tongue, or limb claudication. If untreated, ~40% of patients are at risk of developing permanent visual loss from acute anterior ischaemic optic neuropathy or retinal artery occlusion. There may be signs of temporal artery inflammation on examination, and erythrocyte sedimentation rate (ESR) and CRP are elevated. Mild anaemia and thrombocytosis and elevated liver enzymes are also common.

Treatment

Acute

- First line:
  - if no visual symptoms—PO prednisolone 1mg/kg (max 60mg) daily for 2 weeks, then gradually taper;
  - if visual symptoms—IV methylprednisolone 0.5–1g daily for 3 days, followed by PO prednisolone, as above;
  - consider aspirin 75mg daily.

Maintenance

- First line: PO prednisolone.
- Second line: methotrexate, azathioprine, or cyclophosphamide

Once the diagnosis is suspected, temporal artery biopsy (± ultrasound) should be obtained, and corticosteroid treatment started immediately. The European League Against Rheumatism (EULAR) guidelines recommend acute treatment, as above, subsequently reducing prednisolone by 10mg every 1–2 weeks to 30mg daily, then reducing by 2.5mg every 2 weeks to 10mg daily, and then tapering by 1mg every month, titrating to clinical response and ESR. Some clinicians give aspirin acutely. After a mean duration of treatment of 2 years, cessation of treatment may be attempted. Steroid-sparing immunotherapy may be required if steroid tapering is slow and side effects ensue.

Evidence base

The advantage of high-dose IV steroids over PO prednisolone is disputed but both significantly reduce the subsequent risk of visual loss. Large retrospective cohort studies support the use of low-dose aspirin for suppressing platelet function and preventing cerebrovascular events. Methotrexate 15–25mg/week has the best evidence base as a steroid-sparing agent. Although not yet licensed for use in GCA, interleukin (IL) 6 receptor antagonists show early promise.

Behçet's disease

Behçet's disease is a chronic relapsing multisystem disorder with mucocutaneous, ocular, vascular, and CNS manifestations. Pathology is primarily a venulitis. Neurological involvement occurs in up to 50%, most often in the form of meningoencephalitis, seizures, cortical venous sinus thrombosis, or myelopathy.

Treatment

- First line: prednisolone 1mg/kg/day for 1 month, then taper.
- Second line: cyclophosphamide (IV 750mg to 1g/m^2 monthly or PO 2mg/kg/day), azathioprine (2.5mg/kg/day), or methotrexate (7.5mg weekly).
- Third line: infliximab for refractory disease.
- Thrombotic complications: heparin ± long-term anticoagulation.

Evidence base

EULAR guidelines recommend prednisolone, as above. There is no significant evidence base for efficacy of cyclophosphamide, azathioprine, or methotrexate. Case studies support the use of TNF antagonists, notably infliximab.

Cerebral venous sinus thrombosis is treated acutely with either IV unfractionated heparin or SC LMWH, given together with a short course of glucocorticoids. The benefit of lifelong anticoagulation or antiplatelet agents in those with thrombotic complications remains to be ascertained, and practice varies.

Other conditions

1. *Sjögren's syndrome*: rarely CNS involvement occurs in Sjögren's syndrome in the form of TM or NMO, with which there is an overlap. More commonly, the peripheral nervous system (PNS) is involved (see p. 106).
2. *Secondary CNS vasculitis*: can occur in the setting of a variety of systemic disorders, including connective tissue diseases, infections (viruses, bacteria, fungi, rickettsia, mycoplasma, and protozoa; infectious endocarditis), systemic vasculitides, autoimmune disorders, and drug use (typically sympathomimetics and drugs of abuse).

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Chapter 7

Disorders of peripheral nerves and motor neuron disease

Introduction

The commonest disorders of the peripheral nerves encountered in clinical practice are the chronic length-dependent axonal polyneuropathies seen in association with diabetes mellitus, alcohol overuse, and, worldwide, leprosy (see Table 7.1 for a comprehensive list) as well as the entrapment mononeuropathies. Chronic neuropathies are classified as primarily demyelinating or axonal, on the basis of electrodiagnostic or pathological criteria. Management of chronic axonal neuropathies generally involves treatment of the underlying cause, which may result in stabilization or resolution of the neuropathy (e.g. optimal diabetes control, abstinence from alcohol, withdrawal of causative medication). Demyelinating neuropathies are further classified as hereditary or acquired, the acquired neuropathies being immune-mediated and thus amenable to treatment. Their management is the focus of much of this chapter. The management of vasculitic neuropathy, Bell's palsy, and motor neuron disease (MND) are also included in this chapter.

Table 7.1 Causes of polyneuropathies

Chronic axonal polyneuropathy	Chronic demyelinating polyneuropathies	Acute polyneuropathies
Diabetes mellitus	Chronic inflammatory demyelinating polyradiculo-neuropathy (CIDP)	Guillain–Barré syndrome (GBS)
Alcohol	Multifocal motor neuropathy with conduction block (MMN)	Rabies and post-rabies vaccine
Uraemia	Paraproteinaemic neuropathy	Diphtheria
Cirrhosis	Hereditary polyneuropathies	Heavy metals, industrial toxins
Amyloidosis (associated with plasma cell dyscrasia/myeloma)		Drugs (see Chapter 18, Drugs causing neurological disease)
Hypothyroidism		Acute intermittent porphyria
Acromegaly		Vasculitic neuropathy
Toxins (acrylamide, arsenic, lead, mercury, thallium, organophosphates, carbon disulfide, organic solvents)		Critical illness neuropathy
Drugs (see Chapter 18, Drugs causing neurological disease)		Thiamine deficiency
Deficiency syndromes—primarily B vitamins		Lymphomatous neuropathy
Paraneoplastic		
Hereditary—Charcot–Marie–Tooth disease type 2 (CMT2), amyloidosis, Fabry, porphyria, Refsum		
Infection—leprosy, HIV		
Idiopathic		
Rare—Sjögren's syndrome, vasculitis, sarcoidosis		

Guillain–Barré syndrome

GBS is the major cause of acute neuromuscular paralysis in the developed world. Two-thirds of cases are preceded by an upper respiratory or gastrointestinal infection, the most commonly identified being *Campylobacter jejuni* gastroenteritis. The usual presentation is of a few days' history of sensory symptoms, followed by a progressively ascending flaccid weakness and areflexia, often with back pain, cranial nerve involvement, and autonomic dysfunction. The nadir is usually reached within 2 weeks and by definition at a maximum of 4 weeks.

The CSF is usually acellular, with an elevated protein level. Nerve conduction studies may be normal in early AIDP or show proximal block in the form of prolonged F waves. In established AIDP, small action potentials, prolonged distal motor latency (DML), delayed F waves, and conduction block are seen. Antiganglioside antibodies (mostly anti-GM1) are detected in 25%.

Most cases are monophasic, and only 3% ever relapse. A slow recovery over weeks or months is the rule, and 80% of patients regain the ability to walk independently at 1 year. The mortality rate remains 5%. Only a very small proportion of patients go on to develop a relapsing disease course, requiring a retrospective revision of the original diagnosis to CIDP.

Acute inflammatory demyelinating polyneuropathy variants

Rare subtypes include purely axonal forms, such as *acute motor axonal neuropathy* (*AMAN*), often associated with anti-GD1a and GM1 immunoglobulin G (IgG), and *acute mixed sensory and motor neuropathy* (*AMSAN*). The rare *Miller Fisher* variant of AIDP presents with ophthalmoplegia, areflexia, and sensory ataxia. Anti-GQ1b antibodies are present in over 95% of cases of Miller Fisher syndrome. Several focal 'forme fruste' GBS variants are also described.

Treatment of acute inflammatory demyelinating polyneuropathy

Supportive care

- Monitoring: vital capacity, cardiac rhythm, and BP.
- VTE prophylaxis: thromboembolic deterrent stockings or SC heparin as per local guidelines.
- Analgesia for neuropathic pain: amitriptyline 10mg daily or gabapentin 300mg daily.

Disease-modifying treatment

- PLEX, five plasma volumes over 1–2 weeks, or IVIg 0.4g/kg/day for 5 days.
- Corticosteroids are not of benefit.
- All patients who are not ambulant within 2 weeks of onset should receive IVIg (0.4g/kg/day for 5 days) or PLEX (five plasma volumes over 1–2 weeks). Both treatments hasten recovery, but IVIg is often preferred due to ease of administration. Many clinicians would give IVIg to ambulant, but disabled, patients, particularly in the early stages when there is continuing disease progression.

Table 7.2 Acute treatment of GBS—PLEX vs IVIg

Modality	PLEX	IVIg
Advantages	Can be used in significant renal impairment and true IgA deficiency	More likely to complete course of treatment Easier to administer
Disadvantages	Relative contraindication in patients with haemodynamic instability. Often impractical	Costly
Complications	Sepsis, hypotension, vascular access difficulties	Aseptic meningitis, acute renal failure

Evidence base

Several large RCTs have demonstrated superiority of PLEX over supportive care alone in terms of improving median time to walking with aid. It is of greatest benefit if instituted within 7 days, and four exchanges have been shown to be superior to two. Head-to-head trials have shown equivalence of IVIg to PLEX in hastening recovery. Combining the two treatments does not confer additional benefit. In patients who do not benefit from one course of treatment, a further course of the same modality is recommended. The choice between PLEX and IVIg is guided by local availability and patient co-morbid factors (see Table 7.2). There is no evidence that corticosteroids or any other immunomodulatory treatments are of benefit in GBS.

Chronic inflammatory demyelinating polyneuropathy

CIDP is the commonest acquired cause of chronic demyelinating neuropathy. It occurs with a prevalence of 1–9 per 100 000 and is commoner in older males. It is immune-mediated, and pathogenic antibodies are increasingly thought to play a role in aetiology. CIDP resembles GBS clinically but has a more protracted course progressing over months–years. A history of preceding infection is not generally seen. There is usually symmetrical, proximal and distal weakness affecting the legs more than the arms, glove and stocking sensory loss with impairment of vibration and position sense, and areflexia. Two-thirds subsequently develop a gradual or stepwise progressive course, and one-third relapse and remit. CSF protein is elevated in the presence of a normal CSF white cell count (WCC). Neurophysiology shows slowing of nerve conduction or partial conduction block with prolongation of DMLs and prolonged or absent F waves.

Chronic inflammatory demyelinating polyradiculoneuropathy variants

Whether CIDP is a disease or a syndrome remains controversial. A number of atypical variants exist, including motor and sensory predominant forms, *MADSAM/Lewis–Sumner syndrome* (multifocal acquired demyelinating sensory and motor neuropathy), *distal acquired demyelinating symmetric neuropathy* (*DADS*) with immunoglobulin M (IgM) paraprotein ± anti-MAG antibodies, CIDP with CNS involvement, and *CANOMAD* (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies). CIDP is also seen in association with a variety of systemic disorders, including diabetes mellitus, paraproteinaemia (monoclonal gammopathy of undetermined significance (MGUS), plasma cell dyscrasias), HIV infection, chronic hepatitis B or C, SLE or other connective tissue diseases, sarcoidosis, Lyme disease, inflammatory bowel disease, lymphoma, nephrotic syndrome, organ and bone marrow transplants, and thyrotoxicosis.

Treatment of chronic inflammatory demyelinating polyradiculoneuropathy

- First line: periodic IVIg (2g/kg over 2–5 days), prednisolone (1–1.5mg/kg/day), or periodic PLEX (4–6 exchanges over 8–10 days).
- Second line: azathioprine (2–3mg/kg/day, starting at 50mg od and increasing weekly by 50mg), methotrexate (7.5–15mg weekly), mycophenolate mofetil (1g bd), or ciclosporin.

Evidence base

The majority of patients with CIDP improve with corticosteroids, periodic IVIg, or PLEX. IVIg improves disability in CIDP for 2–6 weeks. Due to the short-lived effects of IVIg, up to 85% of patients will require maintenance dosing at intervals of 2–6 weeks; at this point, doses may be tapered to 1g/kg over 1–2 days. The benefits of corticosteroid therapy in CIDP have long been acknowledged, but there have been few large-scale controlled trials in this area. There is currently no consensus on

the optimum corticosteroid dosing regimen or route of administration. PLEX is effective for short-term treatment of CIDP. Cross-over trials have shown no difference in short-term efficacy between IVIg and PLEX, or between IVIg and corticosteroids. Choice of first-line therapy is guided by disease severity, treatment availability, side effects, comorbidities, and cost. For severe disease, initial therapy with IVIg or PLEX, rather than corticosteroids, is recommended. Corticosteroids may be more suitable for patients with slower-onset CIDP. There are no robust RCT data available to guide choice of any particular second-line immunomodulatory therapy, and current data do not demonstrate significant benefit from any of these treatments.

Multifocal motor neuropathy

This is a very slowly progressive, pure motor syndrome, causing weakness, wasting, and fasciculation predominantly in the upper limbs. There is characteristic multifocal motor conduction block on neurophysiological testing, without involvement of the sensory nerves. ~50% of cases have circulating IgM antibodies to GM1 ganglioside, which may be pathogenic.

Treatment

- First line: periodic IVIg.
- Second line: rituximab or cyclophosphamide for resistant cases.

More than 80% of patients respond to IVIg. Most patients need 2g/kg every 4–8 weeks. Corticosteroids make MMN worse, and paradoxically PLEX is ineffective.

Evidence base

A recent open-label study of 44 adults with MMN randomized 1:1 to either double-blind treatment of IVIg followed by placebo for 12 weeks each, or the reverse, confirmed significant benefit of IVIg, compared to placebo. Mean maximal grip strength declined 31.38% during placebo and increased 3.75% during IVIg ($p = 0.005$). In 35.7% of participants, Guy's Neurological Disability scores for upper limbs worsened during placebo, and not during IVIg, treatment, whereas the converse was true in 11.9% ($p = 0.021$). Sixty-nine per cent deteriorated and switched prematurely from placebo to open-label IVIg, and 2.4% switched from blinded to open-label IVIg ($p < 0.001$). There are no RCTs of immunosuppressive agents. Cyclophosphamide and rituximab have shown some benefit in case reports of refractory cases.

Paraproteinaemic neuropathies

Reported associations between low levels of paraprotein (MGUS) and peripheral neuropathies are generally regarded as coincidental, with the exception of neuropathies associated with IgM gammopathy and POEMS syndrome.

IgM paraproteinaemic neuropathy with anti-MAG

The acquired demyelinating neuropathy associated with IgM paraprotein comprises an entity distinct from CIDP. Most patients present with paraesthesiae and sensory ataxia followed by sensorimotor deficits of varying severity. In more than 75%, the monoclonal IgM recognizes myelin-associated glycoprotein (MAG) and other peripheral nerve glycolipids.

Treatment

Although generally indolent, those severely affected may respond to immunotherapy with rituximab, or to chemotherapy with the purine analogue fludarabine or cyclophosphamide, or to a combination of immunotherapy and chemotherapy. Corticosteroids and IVIg appear to be of no long-term benefit.

Evidence base

Open-label studies and a 2009 RCT indicate that rituximab is the best agent available, providing long-term benefits to almost 50% of treated patients. A recent retrospective study of 45 patients given rituximab alone or in combination with either fludarabine or cyclophosphamide showed that 80% of patients responded to immunotherapy or immunochemotherapy, but that combination therapy produced a more rapid clinical response. However, a recent RCT did not demonstrate significant benefit from rituximab monotherapy.

POEMS syndrome

POEMS syndrome (*P*olyneuropathy, *O*rganomegaly, *E*ndocrinopathy, *M*onoclonal protein, *S*kin changes) is a rare condition characterized by the presence of a monoclonal plasma cell disorder and peripheral neuropathy, along with other systemic symptoms, elevated serum vascular endothelial growth factor (VEGF) levels, Castleman's disease, and osteosclerotic bone lesions. Treatment is based on that used for multiple myeloma and includes radiotherapy to bony lesions, melphelan, and corticosteroids.

Vasculitic neuropathy

Vasculitis can affect the vasa nervorum of peripheral nerves, causing critical ischaemia of the nerves. Vasculitic neuropathy is usually seen in association with systemic vasculitides (usually those involving small and medium-sized arteries) or connective tissue diseases (rheumatoid arthritis, SLE) which can also involve the skin, lungs, kidney, joints, and other organs. Pathogenesis varies, depending on the underlying condition, but may involve immune complex deposition within vessel walls (prominent in cryoglobulinaemia and polyarteritis nodosa (PAN)), and/or T cell-mediated immune mechanisms (seen in anti-neutrophil cytoplasmic antibody (ANCA)-associated disease). Three patterns of nerve injury are seen in vasculitic neuropathy: mononeuritis multiplex, distal polyneuropathy, and radiculoplexopathy. Onset may be abrupt or insidious; both motor and sensory nerves can be involved, and pain may be prominent.

Systemic vasculitides with peripheral nerve involvement

Systemic vasculitides commonly affecting the peripheral nerves include ANCA-positive vasculitis (e.g. Wegener's (granulomatosis with polyangiitis), microscopic polyangiitis, and Churg–Strauss (eosinophilic granulomatosis with polyangiitis)), PAN, and mixed cryoglobulinaemia. The latter is characterized by the deposition of circulating cryoglobulins in the vasa nervorum and most commonly presents as a selective small-fibre sensory neuropathy. Cryoglobulinaemia is most commonly associated with chronic hepatitis C infection, but other infections (hepatitis B, EBV, HIV), lymphoproliferative malignancies, and autoimmune diseases (SLE, Sjögren's) may also be responsible.

When vasculitic neuropathy is associated with an identifiable systemic vasculitis or connective tissue disease, immunosuppressive therapy is directed at the underlying disease.

Isolated (non-systemic) vasculitic neuropathy

Less commonly, vasculitic neuropathy occurs as a result of isolated PNS vasculitis without evidence of systemic involvement, although, in some cases, systemic vasculitis subsequently emerges.

Treatment of isolated vasculitic neuropathy

Mild disease only

- Induction: prednisolone 1mg/kg/day for 4 weeks, tapering over 6 months.*

* Suggested prednisolone tapering regime. Reduce by 10mg each week to 40mg/day, then by 5mg each week to 20mg/day, then by 2.5mg each week to 10mg/day, then by 1mg every 2 weeks to 5mg/day. Further taper by 1mg every 2 weeks if stable disease.

Moderate to severe disease

- Induction: IV methylprednisolone 1g daily for 3 days, followed by prednisolone 1mg/kg/day for 4 weeks (taper over 6 months*) plus cyclophosphamide PO 2mg/kg daily or IV pulses 750mg/m^2 bovine serum albumin (BSA)** every 4 weeks (plus mesna and trimethoprim–sulfamethoxazole) for 6 months.
- Maintenance: azathioprine (1.5–3mg/kg/day) or methotrexate (initially 15mg/week)—discontinue after 6–12 months' disease-free period.

Evidence base

A 2007 Cochrane database review concluded that there were no adequate RCTs on which to base treatment for non-systemic vasculitic neuropathy. Therefore, therapeutic decisions are based primarily on clinical experience, observational data, and extrapolation from trials of immunosuppressive agents in systemic vasculitis and connective tissue diseases. Because of the toxicity of long-term cyclophosphamide therapy, a number of less toxic drugs have been used for maintenance therapy after disease control has been attained with cyclophosphamide. The use of azathioprine and methotrexate in this context is based upon their proven value as maintenance therapy in Wegener's.

* Suggested prednisolone tapering regime. Reduce by 10mg each week to 40mg/day, then by 5mg each week to 20mg/day, then by 2.5mg each week to 10mg/day, then by 1mg every 2 weeks to 5mg/day. Further taper by 1mg every 2 weeks if stable disease.

** Cyclophosphamide IV pulse should be reduced to 500mg/m^2 if obese, age >70 years, renal impairment, or neutropenia <1.5.

Bell's palsy

Bell's palsy is an acute peripheral facial nerve palsy of unknown cause, which, in most cases, is probably due to herpes simplex virus (HSV) reactivation. It accounts for at least half of all cases of peripheral facial palsy, with an annual incidence of 13–34 per 100000; the risk is increased during pregnancy. Presentation is with sudden-onset unilateral facial paralysis. Hyperacusis and ipsilateral taste disturbance may be present, and rarely ipsilateral facial sensory loss occurs.

Treatment

- First line: prednisolone 50–80mg/day for 7–10 days. Good eye care.
- Second line: consider aciclovir 800mg tds or valaciclovir 1000mg tds for severe facial palsy.

The mainstay of treatment for Bell's palsy is early oral corticosteroid therapy, ideally beginning within 3 days of onset of symptoms. There is no consensus regarding the optimum regimen for corticosteroid therapy, and practice varies, but 7–10 days of treatment is generally given. The use of concomitant antiviral therapy with aciclovir for confirmed Bell's palsy is recommended for severe cases only. The presence of vesicles in the external auditory meatus, however, suggests varicella-zoster reactivation (Ramsay Hunt syndrome), rather than Bell's palsy, and warrants early treatment with an antiviral agent. It is also important to protect the ocular surface from the effects of poor eyelid closure. Regular lubricating eye drops, taped eyelid closure, and sutures may be required in some cases. Ophthalmology review can often be helpful.

Evidence base

There is good-quality evidence of the efficacy of prednisolone in the treatment of Bell's palsy. Prednisolone treatment was shown to significantly reduce the risk of an unfavourable outcome from Bell's palsy by 31% in a large meta-analysis of 2786 patients. An earlier RCT demonstrated a >2-fold greater chance of complete recovery with prednisolone treatment, compared to placebo. A recent randomized prospective study has shown additional benefit of antiviral therapy for acute severe Bell's palsy. Treatment with antiviral agents alone does not significantly improve recovery. There is limited evidence regarding the use of electrical nerve stimulation to promote motor recovery. Although case reports and small case series have suggested some benefit, there have been no controlled trials, and it is not currently recommended.

Sjögren's syndrome

Sjögren's syndrome is an autoimmune disorder characterized by lymphocytic infiltration of the salivary and lacrimal glands. It can occur in a primary form or as a complication of other autoimmune diseases (most commonly rheumatoid arthritis). Diagnosis of Sjögren's syndrome requires the satisfaction of four of six internationally defined criteria: symptoms of dry eyes, positive Schirmer's or Rose Bengal dye test, symptoms of dry mouth, focal lymphocytic sialoadenitis on minor salivary gland biopsy, demonstration of either reduced salivary flow on scintigraphy or diffuse sialectasia on parotid sialography, and serum autoantibodies to Ro (SSA) or La (SSB).

Neurological symptoms occur in 20% of cases. They may precede the characteristic sicca symptoms, and anti-Ro and La antibodies are often absent, making the diagnosis challenging. The commonest neurological manifestations include peripheral neuropathy, usually sensory ganglionopathy or painful small-fibre neuropathy, often with a prominent autonomic component. Occasionally, cranial or multiple mononeuropathies or myelopathy are seen.

Treatment

Immunosuppression is generally necessary for neurological involvement and may include corticosteroids, IVIg, azathioprine, cyclophosphamide, PLEX, infliximab, or rituximab.

Evidence base

There is a lack of high-quality randomized trial data regarding the treatment of neuropathy in Sjögren's syndrome. Small series report efficacy of corticosteroid immunosuppression followed by a course of IVIg at 1–2g/kg given every 2–4 weeks. The largest series to date retrospectively studied 82 patients with neuropathy. The response to corticosteroids was variable, with improvement or stabilization noted in only 45% of patients; corticosteroids were not effective in any patient with polyneuropathy. Treatment with cyclophosphamide (700mg/m^2 IV monthly for 6–12 months) resulted in at least partial recovery in 11 of 12 patients with myelopathy, and in eight of eight patients with multiple mononeuropathy.

Other systemic conditions with peripheral nerve involvement

Sarcoidosis affects the CNS, the PNS, or both. Cranial neuropathies are the commonest manifestation of neurosarcoidosis. Other peripheral manifestations include myopathy and, rarely, peripheral polyneuropathy.

In *SLE*, PNS involvement is less common than CNS disease but includes polyneuropathies, dysautonomias, mononeuropathies, and plexopathies.

Motor neuron disease

MND encompasses a group of conditions characterized by degeneration of the anterior horn cells and central motor pathways. The prognosis is invariably poor, with an average survival of 2–3 years from diagnosis, although there is considerable variation between individuals and phenotypic subtypes—50% of patients die within 30 months of symptom onset; 15–20% are alive at 5 years, and a small percentage survive beyond 10 years

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is the commonest form of MND, accounting for around 70% of cases; 1–2% of these are due to inherited defects in the superoxide dismutase gene (*SOD1*). Onset is usually in the seventh decade of life. The clinical hallmark is mixed upper motor neuron (UMN) and lower motor neuron (LMN) features with muscle weakness, usually pyramidal in pattern, fasciculations, and wasting, brisk reflexes, and extensor plantar responses. About one-third of patients present with upper limb symptoms, one-third with lower limb symptoms, slightly fewer than one-third with bulbar dysfunction, and 1–2% with isolated respiratory failure. Sensory symptoms are rare. Clinically significant frontotemporal dementia occurs in about 5%, but half of all patients have mild executive dysfunction. Neurophysiological investigations showing widespread denervation and reinnervation are important for confirming the clinical diagnosis.

Phenotypic variants of MND include *progressive muscular atrophy* (PMA), a purely LMN variant, often beginning asymmetrically in the legs and associated with a longer median survival of ~5 years. *Primary lateral sclerosis* (PLS) accounts for 1–2% of cases and presents with pure UMN features, although LMN features may develop after ~4 years. It has a slower progression and longer life expectancy than ALS. *Progressive bulbar palsy* is rare, usually affecting women over 65 years, which progresses to complete anarthria over about 12 months and affects the respiratory and limb muscles after 2–4 years. It is distinct from bulbar-onset MND which refers to the one-third of patients who present with bulbar dysfunction prior to generalized spread and which also has a worse prognosis. Other rare forms include *flail arm variant* (also known as brachial amyotrophic diplegia) and lower limb-onset MND.

Treatment

Symptomatic and supportive treatment remains the mainstay of management (see Table 7.3). Enlisting the support of multidisciplinary health professionals, such as physiotherapists, speech therapists, and palliative care specialists, early on is crucial. Non-invasive ventilation can improve quality of life and survival in patients who tolerate it. Insertion of percutaneous gastrostomy tubes for ongoing feeding requirements should be considered. Respiratory failure and chest sepsis are the commonest causes of death in patients with ALS.

Table 7.3 Symptomatic therapies for ALS/MND

Symptom	Treatment
Dysarthria	Speech therapy Whiteboard Electronic communication devices
Sialorrhoea	1% atropine eye drops given sublingually Amitriptyline 10mg nocte Hyoscine hydrobromide 300 micrograms tds or 1mg/24h transdermal patch Glycopyrronium bromide Parotid botulinum toxin/irradiation
Thick pharyngeal secretions	Carbocysteine 375–750mg qds Pineapple juice
Cramps	Carbamazepine (initially 100mg daily) Quinine 300–325mg bd
Spasticity	Baclofen Tizanidine Gabapentin
Emotional lability	Amitriptyline SSRIs
Fatigue	Modafinil 200mg daily

Disease-modifying treatment

- First line: riluzole (50mg bd).

Riluzole, a glutamate receptor antagonist, is the only disease-modifying treatment for ALS and has only a very modest effect on survival.

Evidence base

Riluzole has been shown to increase survival by an average of 3 months if used early in the disease course. Both the EFNS and AAN recommend early treatment with riluzole 100mg daily for ALS. Expert consensus suggests that riluzole is of uncertain benefit for other forms of MND, although it is used off-licence in these conditions.

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Chapter 8

Disorders of muscle and neuromuscular junction

Introduction

Muscle disorders comprise a diverse group of conditions. Immunosuppressive treatments are effective for those disorders with an inflammatory component such as the inflammatory myopathies and the autoimmune channelopathies. Several conditions respond well to symptomatic therapies. Disease modifying therapy (DMT) is not available for many, but modern molecular genetics techniques show early promise. Disorders of the neuromuscular junction (NMJ): myasthenia gravis (MG), and Lambert–Eaton syndrome, are also included in this chapter.

Inflammatory myopathies

Inflammation is seen in many muscle diseases, but those in which inflammation is the prime pathogenic process are termed inflammatory myopathies. The inflammatory myopathies are a heterogeneous group of acquired disorders.

Polymyositis and dermatomyositis

Polymyositis (PM) and dermatomyositis (DM) are the commonest acquired inflammatory myopathies but are still rare, with a combined incidence of 2 in 100000. Both occur more commonly in females and between the ages of 40 and 50, but individuals of any age may be affected. Patients may report insidious or subacute onset of proximal, usually symmetrical, weakness, with gradual worsening over a period of several months. However, an acute onset of weakness is occasionally reported. There may be myalgia, dysphagia, and neck flexion weakness, and rarely facial or respiratory muscle involvement. Serum creatine kinase (CK) is usually elevated (up to 100 times normal). In DM, skin changes precede or accompany the weakness and include heliotrope rash, with eyelid oedema, photosensitive erythematous rash on exposed areas, and Gottron's papules on knuckles. Subcutaneous calcification and contractures can occur in affected children.

There is an association with malignancy, particularly in DM where the incidence of cancer is increased 5- to 7-fold. Up to 70% of such cancers are of the cervix, lung, pancreas, bladder, ovaries, or stomach, and these confer a worse prognosis. Cancer should be screened for in all patients over the age of 40 years and in treatment-resistant cases.

Definitive diagnosis is with muscle biopsy which shows muscle fibre necrosis, degeneration, regeneration, and an inflammatory cell infiltrate. In DM, there is perivascular B cell-mediated inflammation, and in PM intrafascicular infiltration with cytotoxic T cells.

Treatment

Treatment of associated malignancy may lead to amelioration of the inflammatory myopathy. Both PM and DM may respond to treatment with corticosteroids alone, but often a combination of steroids and an immunosuppressive agent is required to achieve satisfactory disease control. Up to 80% of patients respond to corticosteroid therapy alone. Care should be taken to avoid secondary steroid myopathy, more likely if high doses (>25mg/day prednisolone) are given for too long (2–3 months) and suggested by increasing weakness despite normalization of CK levels.

Initial treatment/induction

- First line: PO prednisolone (1mg/kg/day, maximum 80mg/day) for 3–6 weeks, then gradually tapering according to clinical response and CK level, aiming to wean off by 1 year.
- IV methylprednisolone (0.5–1g daily for 3–6 days) can be given initially for severe disease, prior to prednisolone as above.

Maintenance

- First line: azathioprine (2–3mg/kg/day) or methotrexate (10–20mg/week).
- Second line (resistant disease): rituximab (750mg to 1g/m^2/week for 2 weeks) or IVIg (2g/kg over 3 days, followed by monthly 3-day courses); azathioprine combined with methotrexate; or mycophenolate mofetil (0.5–1g bd) combined with azathioprine or methotrexate.
- Third line: ciclosporin (3–5mg/kg/day), tacrolimus (0.1mg/kg/day), or cyclophosphamide (2- to 4-weekly IV pulses of 0.5–1g).

Evidence base

Corticosteroid therapy predominates, despite a lack of good-quality evidence for its use. Methotrexate or azathioprine appear to be equally effective as maintenance therapy and can be started concurrently with steroids or if steroid monotherapy proves insufficient. No head-to-head trials have compared the two agents. Patients on a combination of prednisolone and azathioprine had improved functional outcomes at 3 years compared to prednisolone alone, and retrospective studies have shown response rates of up to 80% with methotrexate.

Despite a lack of good-quality evidence, combinations of azathioprine and methotrexate or either agent plus mycophenolate are occasionally given for refractory cases.

For severe refractory disease, rituximab has demonstrated efficacy in a large placebo-controlled trial, and IVIg has shown effective short-term improvement of resistant myositis in a modest number of trial patients. IVIg is regarded as second-line therapy for DM by some experts, on the basis of the putative role of B cells and autoantibodies in this condition. The evidence base for calcineurin inhibitors and mycophenolate for refractory inflammatory myopathy is weaker and predominantly retrospective. Cyclophosphamide should only be considered in patients refractory to other second-line agents, due to its toxicity. Experience is still limited with TNF-α antagonists such as infliximab or etanercept.

Inclusion body myositis

This is the commonest acquired muscle disease over the age of 50 years, more prevalent in men and classically occurring in the sixth decade of life. It is characterized by an insidious, painless, symmetrical weakness, initially affecting proximal leg muscles. There is a distinct pattern of weakness, with selective involvement of quadriceps, foot extensors, and forearm finger flexors. Facial weakness and dysphagia are common. Muscle biopsy shows characteristic rimmed vacuoles and muscle fibre inclusions, as well as evidence of cytotoxic T cell-mediated inflammation.

Treatment

- First line: Supportive treatment without active immunosupression.
- Second line: Consider a 6 month trial of prednisolone (1mg/kg/day), azathoprine (1.5–2.5mg/kg/day), or methotrexate (7.5mg/week) as steroid sparing agents if prednisolone has sustained effectiveness.

Evidence base

Compared to other inflammatory myopathies, inclusion body myositis (IBM) is relatively resistant to immunosuppressive treatment. A minority of patients may respond to treatment with corticosteroids and immunotherapy, but eventual progression is not prevented. Several non-randomized studies have shown little benefit from prednisolone, even when given early, for improving muscle strength. Nonetheless, some clinicians would consider a 3- to 6-month trial of prednisolone and methotrexate or azathioprine if the patient's muscle biopsy shows prominent inflammation and muscle weakness is not advanced. There is no evidence to support the use of one second-line therapy over another.

Other inflammatory myopathies

Several other myopathies may show inflammatory changes on biopsy, including granulomatous myositis, overlap myositis, necrotizing myopathy due to cancer, necrotizing autoimmune myopathy (NAM), and certain forms of muscular dystrophy. In the absence of adequate, controlled treatment trials, therapy of this group remains empirical with corticosteroids and steroid-sparing agents.

Mitochondrial myopathies

Defects in the respiratory chain of enzymes impairing oxidative phosphorylation is the key feature of mitochondrial disorders. Myopathy, often proximal, is one clinical aspect of these multisystem disorders, which have a wide spectrum of clinical features, including short stature, ataxia, ophthalmoplegia, deafness, epilepsy, and cardiac conduction defects. Diagnosis involves a combination of histological and genetic testing. Typical features on muscle biopsy include intermyofibrillar or subsarcolemmal aggregates of mitochondria, and 'ragged red fibres' due to subsarcolemmal accumulations of mitochondria (which stain red with Gomori trichrome). Treatment options are limited, although there are a few therapies with a limited evidence base that can be used (see Treatment, p. 116). Certain drugs should be avoided (see Table 8.1).

Treatment

Acute treatment of stroke-like episodes in mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)

- There are currently no specific treatments with proven efficacy in stroke-like episodes of mitochondrial origin. Management is supportive including aggressive seizure control (avoiding valproate), adequate hydration and nutrition, and treatment of any triggering systemic illness. Some use *L*-arginine 500mg/kg IV infusion every 6h for up to 3 days although the evidence base for this is poor. Early liaison with a specialist unit is advised. In the UK: www.mitochondrialncg.nhs.uk.

Adjunctive treatment of mitochondrial myopathies

- Respiratory chain cofactors: coenzyme Q10 (CoQ10) 5–30mg/kg daily, maximum 1200mg daily, is often trialled, it may be of benefit in patients with mitochondrial myopathy due to CoQ10 deficiency.
- Exercise programmes are safe and moderately effective.
- Identification and management of systemic manifestations of mitochondrial disease including cardiac arrythmias and gastrointestinal dysmotility.

Evidence base

Many agents have been trialled in mitochondrial disease including antioxidants, levocarnitine (*L*-carnitine), creatinine, riboflavin, and folate. Their

Table 8.1 Drugs to avoid in mitochondrial myopathies

Drug	Comment
Barbiturates Chloramphenicol Sodium valproate Tetracyclines	Interfere with respiratory chain function
Metformin	Potential for exacerbating lactic acidosis
Aminoglycosides	Increased risk of hearing loss

effectiveness has not been borne out in small studies or clinical practice. Exercise programmes do improve quality of life, strength, and fatigue either as a result of reversal of muscular deconditioning or through direct effects on mitochondrial function.

Mitochondrial disease is a multisystem disorder and cardiac and other organ manifestations are potentially life-threatening. These should be screened for and managed depending on the underlying molecular diagnosis.

With regards specific therapies trialled in mitochondrial disease: *L*-arginine is a naturally occurring amino acid which is the physiological precursor of nitric oxide (NO). It has an important role in endothelial vascular relaxation, which may underlie its mechanism of action. A single non-randomized trial involving 24 patients showed that *L*-arginine significantly reduced symptoms (headache, nausea, vomiting, teichopsia) during acute stroke-like episodes. Six patients underwent prophylactic administration of *L*-arginine over a period of 18 months, and none had a major stroke-like syndrome following this. Further larger studies are required to verify the potential significance of this.

CoQ10 is an endogenous compound essential for aerobic cellular respiration, first used as a treatment for mitochondrial disease in 1986. It is involved in transfer of electrons between enzyme complexes I, II, and III of the electron transfer chain at the inner mitochondrial membrane and is also an effective oxygen free radical scavenger. A recent randomized trial evaluated the efficacy of CoQ10 in 30 patients with mitochondrial cytopathy. Compared to placebo, CoQ10 significantly reduced venous lactate after exercise, but clinically relevant endpoints, such as muscle strength, were unaffected. A small meta-analysis including eight trials found no clear evidence to support the use of pharmacologic therapy for mitochondrial disease.

Muscular dystrophy

The muscular dystrophies are a group of inherited genetic disorders characterized by muscle wasting and weakness due to mutations in a number of genes required for normal muscle function. Only the commonest, Duchenne muscular dystrophy (DMD) has shown partial response to DMT and is discussed below. Becker muscular dystrophy is less common and has a similar, but milder, phenotype. Other rare dystrophies include facioscapulohumeral dystrophy, the genetically heterogeneous limb girdle and Emery–Dreifuss muscular dystrophies, and distal and oculopharyngeal muscular dystrophies. There is a distinct lack of evidence base for efficacy of corticosteroids or other DMTs for any of these conditions. Gene transfer and exon skipping strategies are undergoing evaluation.

Duchenne muscular dystrophy

DMD is an X-linked disorder caused by mutations in the dystrophin gene. It affects 1 in 3500 males and presents with delayed motor milestones in childhood due to proximal muscle weakness. Calf pseudohypertrophy and mild cognitive impairment are other features. Systemic complications include scoliosis, respiratory muscle weakness, dilated cardiomyopathy, and cardiac conduction deficits which may lead to cardiac failure. Mean age at loss of ambulation is 9 years (range 6–15 years), electric wheelchair dependency 14 years (range 11–28 years), needing assistance for eating and drinking 18 years (range 12–23 years), and requiring assisted ventilation 19 years (range 14–31 years). Estimated median survival is 35 years. CK is elevated (but may fall to normal levels in adult life). Muscle biopsy shows fibre necrosis and replacement with fat and fibrosis with an absence of dystrophin.

Treatment

- Disease modification: prednisolone 0.75mg/kg/day or deflazacort 0.9mg/kg/day.
- For ventricular dysfunction: ACE inhibitor and/or β-blocker.
- Bone protection: calcium and vitamin D3.

Survival, neuromuscular function, and quality of life in DMD are improving due to longer-term treatment with glucocorticoids, advances in respiratory care, and increased utilization of assisted ventilation. Boys 5 years of age and older, who are no longer gaining motor skills or whose motor skills are declining, are usually treated with prednisolone (0.75mg/kg/day, or 10mg/kg a week given over 2 weekend days) or deflazacort (0.9mg/kg/day). An ACE inhibitor and/or β-blocker is indicated if there is evidence of ventricular dysfunction, and bone protection is also required. A stepwise sequence of respiratory interventions is recommended by current guidelines.

Evidence base

In 2005, the AAN, and in 2008 a Cochrane review, evaluated all RCTs examining the use of corticosteroids in DMD and concluded that prednisone at doses of 0.75mg/kg/day caused an increase in muscular strength and improved results in standardized functional tests in the short term. Five long-term controlled, non-randomized trials (extending beyond 3 years) with prednisone or deflazacort found that patients can ambulate 2–5 years longer than those not receiving corticosteroids, the need for spinal stabilization surgery was reduced, and the need for non-invasive ventilation delayed. Recent non-randomized trials indicate that corticosteroids may delay the onset of cardiomyopathy. Trials of other immunosuppressive agents (azathioprine, ciclosporin) have not demonstrated any benefit.

Myotonic dystrophy

Myotonic dystrophy is an autosomal dominant inherited disorder characterized by muscle wasting and myotonia (the phenomenon of delayed relaxation of skeletal muscles after voluntary contraction). Myotonic dystrophy type 1 (DM1, dystrophia myotonica, Steinert's disease) is the commonest cause of adult muscular dystrophy, with a prevalence of 3–15 in 100000. There is a characteristic facial appearance with ptosis, temporal wasting, 'hatchet' facies, and frontal balding. Patients also have sternocleidomastoid and distal limb weakness and wasting. Less commonly, bulbar, respiratory, and extraocular muscles are involved. Myotonia is exacerbated by cold and stress and is usually most pronounced in the face, jaw, tongue, and hands. Associated cardiac pathology (arrhythmia, structural abnormalities, and sudden cardiac death) and impaired respiratory function account for up to 75% of mortality. Cataracts and diabetes mellitus are common comorbid conditions. Myotonic dystrophy type 2 (DM2, proximal myotonic myopathy (PROMM)) is a less severe disease with proximal muscle weakness, particularly of the hip girdle muscles, myalgia, stiffness, and fatigue. Definitive diagnosis is by genetic testing, which shows a CTG trinucleotide expansion in DM1 and a CCTG tetranucleotide expansion in DM2.

Treatment

There is currently no effective DMT, and management is supportive. Annual ECG should be performed, and periodic cardiac and respiratory assessments are important.

- For myotonia (rarely required): mexiletine (150–200mg tds), imipramine (150–200mg daily), clomipramine (75mg daily), carbamazepine (up to 600mg bd), or phenytoin (150–200mg daily).
- For daytime somnolence: modafinil (200–400mg/day).
- Drugs to avoid: General anaesthesia increases the risk of postoperative aspiration pneumonia and cardiac arrhythmia in patients with myotonic dystrophy.

Evidence base

Mexiletine is superior to placebo in improving grip relaxation time in patients with DM1, as shown by two small randomized trials. In one, mexiletine 150–200mg tds significantly reduced grip relaxation time. Two small controlled trials from the late 1980s demonstrated the utility of imipramine and clomipramine. Systematic reviews, however, have not found sufficient evidence to support the use of any drugs for myotonia. Mexiletine and TCAs should be used with caution, in view of the risk of cardiac conduction abnormalities.

Inherited non-dystrophic myotonias

The non-dystrophic myotonias are a heterogeneous set of rare skeletal muscle channelopathies that demonstrate clinical and/or electrical myotonia, and are distinct from myotonic dystrophy. They include the myotonia congenita disorders and paramyotonia congenita.

Myotonia congenita

Myotonia congenita (congenital myotonia) is caused by mutations in skeletal muscle voltage-gated chloride channel gene (*CLCN1*), resulting in reduced chloride conductance. *Thomsen's disease* is transmitted by autosomal dominant (AD) inheritance, and *Becker's disease* by autosomal recessive (AR) inheritance. Membrane hyperexcitability leads to repetitive firing of muscle fibres, which summate to give clinical myotonia. Myotonia develops following voluntary muscle contraction, often triggered by cold, stress, fatigue, or hunger. Sufferers demonstrate the 'warm-up' phenomenon of improved movement after a few contractions. Patients often have an athletic physique due to muscle hypertrophy from constitutive contraction.

Paramyotonia congenita

Paramyotonia congenita (Eulenburg's disease) is caused by AD transmitted mutations in the *SCN4A* gene, which encodes a skeletal muscle voltage-gated sodium channel. The cardinal feature is exercise- or cold-induced myotonia, which, along with stiffness, worsens with ongoing exercise. This typically affects the eyelids, face, tongue, neck, and hands. CK is elevated, and EMG shows a significant fall in CMAP amplitude in cold conditions. Patients should be advised to avoid exercising in cold conditions.

Treatment

- First line: mexiletine 150–200mg tds.
- Second line: carbamazepine up to 600mg bd or phenytoin 100–250mg daily.
- Third line: imipramine 150–200mg/day or clomipramine 75mg/day.
- Drugs to avoid in myotonia: clofibrate, cholinesterase inhibitors, propofol, propranolol, and suxamethonium.

Evidence base

Due to the rarity of these conditions, there is a paucity of robust evidence regarding treatment. Nonetheless, a multicentre RCT of 59 patients with non-dystrophic myotonia showed that mexiletine significantly improved stiffness, handgrip myotonia, and quality of life after a 4-week treatment course. There is little controlled trial evidence to support the use of phenytoin and carbamazepine, but clinical experience supports their effectiveness when mexiletine fails. Small placebo-controlled cross-over studies have demonstrated improvement of myotonia with imipramine and clomipramine.

Periodic paralyses

Hypokalaemic periodic paralysis

Hypokalaemic periodic paralysis is caused by several different rare AD mutations of genes coding for skeletal muscle calcium (*CACNA1S* in 70% of patients), sodium (*SCN4A*), and potassium (*KCNE3*) channels. Thyrotoxicosis, renal tubular acidosis, and chronic potassium loss can cause a similar picture. Incidence is ~1 in 100000. Attacks of extreme generalised weakness lasting hours to days can occur, in association with a fall in serum potassium to <2mmol/L. Attacks are precipitated by carbohydrate- or sodium-rich foods, rest after exertion, cold, and alcohol. Interictally, there is no myotonia and a normal serum potassium. Patients may develop proximal weakness in their 40s or 50s, by which time the acute attacks tend to subside.

Treatment

Acute attacks

- PO potassium replacement: 30mEq potassium chloride (KCl) every 30min, until serum potassium normalizes. Serum potassium should be monitored for 24h to assess for rebound hyperkalaemia.

Prophylaxis of attacks

Attacks may be prevented by a low-carbohydrate diet and abstinence from vigorous exercise.

- First line: carbonic anhydrase inhibitors (acetazolamide 250mg bd or diclofenamide 50mg bd).
- Second line: potassium-sparing diuretics (spironolactone 100mg daily or triamterene 150mg daily).

Evidence base

Carbonic anhydrase inhibitors reduce frequency and severity of attacks in most patients. However, in 10% of patients, they may have a paradoxical effect of worsening symptoms by potentiating potassium uptake into muscle. This risk is increased with comorbid diabetes and thyrotoxicosis. Diclofenamide has a significantly beneficial effect on attack frequency and severity, with a milder side effect profile than acetazolamide, but is not available in the USA and most European countries. As second-line therapy, potassium-sparing diuretics may be useful alternatives.

Hyperkalaemic periodic paralysis

Hyperkalaemic periodic paralysis is caused by an AD inherited mutation of *SCN4A*, a component of skeletal muscle sodium channels. Incidence is 1 in 200000. Attacks of episodic generalized or focal weakness and myotonia begin in childhood, increase in frequency up to age 50, and decline thereafter. Attacks occur in association with a rise in serum potassium to >5mmol/L. They commonly occur on waking and last for up to an hour. Interictally, myotonia is present in some patients, but serum potassium is normal.

Treatment

Acute attacks

Attacks are brief and often do not need treatment per se. One to two puffs of salbutamol may attenuate attacks. Severe hyperkalaemia should be treated as per local protocols.

Prophylaxis of attacks

Attacks may be prevented by frequent carbohydrate-rich meals, and avoidance of fasting, dietary potassium, or drugs known to increase serum potassium.

- First line: carbonic anhydrase inhibitors (acetazolamide 250mg bd or diclofenamide 50mg bd).
- Second line: thiazide diuretics, e.g. hydrochlorothiazide 25–50mg/day.

Evidence base

Diclofenamide was shown to significantly reduce the rate and severity of attacks of hyperkalaemic periodic paralysis in a randomized, double-blind cross-over trial of 31 patients. Acetazolamide and thiazide diuretics have only anecdotal evidence of efficacy in this setting.

Acquired neuromyotonia

Acquired neuromyotonia, also known as *Isaac's syndrome* is a very rare condition characterized by painful cramps and impaired muscle relaxation with or without autonomic dysfunction. There are pathogenic autoantibodies to CASPR2, a component of the voltage-gated potassium channel, and strong associations with myasthenia and thymoma. *Morvan syndrome*, a related condition, refers to a combination of symptoms of neuromyotonia (cramps and fasciculation), autonomic dysfunction, and CNS involvement with insomnia and hallucinations, which is also associated with CASPR2 antibodies. Thymoma is associated in 50%, and thymectomy may be curative. Both conditions respond well to immunotherapy. The EFNS guidelines suggest similar immunomodulatory regimens to those established for MG. Anticonvulsants can relieve symptoms by reducing peripheral nerve hyperexcitability.

Stiff person syndrome

Stiff person syndrome is a rare disorder characterized by fluctuating rigidity and stiffness of the axial and proximal leg muscles, producing hyperlordosis due to lumbar paraspinal and abdominal muscle co-contraction, with superimposed painful spasms and continuous motor activity on EMG. Most cases have circulating autoantibodies against glutamic acid decarboxylase (GAD), but there are also paraneoplastic varieties. Common associations include diabetes mellitus and psychiatric disorders.

Treatment

Symptomatic

- First line: diazepam 5–100mg daily in divided doses; clonazepam 1–6mg daily; baclofen 20mg tds.
- Second line: gabapentin, levetiracetam, sodium valproate.

Immunosuppression

- First line: prednisolone 60mg daily, then taper; periodic IVIg.
- Second line: PLEX, rituximab.

Symptomatic treatment with GABA-ergic or other antispasmodic agents is generally effective. Benzodiazepines are considered the optimal initial therapy, but large doses may be required. If escalating doses of benzodiazepines are not tolerated, baclofen (20mg bd to tds) can be added or substituted.

Immunomodulation with prednisolone (60mg daily, tapering according to response), periodic IVIg or PLEX or rituximab should be considered in severe or refractory cases.

Evidence base

Striking efficacy of diazepam was first reported in the 1960s. There are no studies to guide the choice of benzodiazepine. Efficacy of IVIg was demonstrated in a cross-over study comparing placebo with IVIg therapy. 11 of 16 patients who received immunoglobulin were able to walk more easily or without assistance, had fewer falls, were able to perform work-related or household tasks, and anti-GAD antibody titres declined. Roughly half of patients with refractory stiff person syndrome described in case reports and case series experienced clinically significant improvement with PLEX.

Disorders of the neuromuscular junction

Myaesthenia Gravis (MG) is by far the commonest NMJ disorder. Lambert–Eaton myasthenic syndrome (LEMS) is also discussed here, and NMJ dysfunction due to *Clostridium botulinum* infection is covered in Chapter 15, Neurological infection.

Myasthenia gravis

MG is the archetypal antibody-mediated autoimmune disorder and the commonest disease affecting the NMJ, with a prevalence of 15 in 100000. Up to 90% of cases have circulating pathogenic autoantibodies directed against the nicotinic acetylcholine receptor (nAChR) at the post-synaptic membrane, and 30–40% of nAChR-negative cases have muscle-specific kinase (MuSK) antibodies. Myasthenia is twice as common in females and has a bimodal age of onset. Early-onset disease typically affects women under 40, whereas late-onset myasthenia is commoner in older men, but age of onset can range from 2 to 90 years. Thymic hyperplasia (less frequently thymoma) is seen in the majority of early-onset cases, and thymectomy is curative in a proportion.

The typical clinical picture is of fatigable ptosis, external ophthalmoparesis, and bulbar, facial, jaw, neck, and proximal limb weakness. Two broad categories are described: ocular (15% of cases) and generalized, reflecting the extent of clinical involvement. There is potential for neuromuscular respiratory failure, so regular forced vital capacity (FVC) monitoring should be undertaken in patients with uncontrolled disease.

Diagnosis is primarily clinical and serological, but bedside testing with the ice pack or edrophonium tests can be a useful adjunct. Characteristic neurophysiological findings are decremental compound muscle action potentials (CMAPs) on repetitive nerve stimulation and increased jitter and block on single-fibre EMG. CT or MRI thorax is required to exclude thymic hyperplasia or thymoma.

Treatment

Symptomatic therapy

- First line: pyridostigmine 30–90mg every 4–8h.

Immunomodulatory therapy

Acute/induction

- First line: prednisolone.
- Second line: IVIg.

Also see Myasthenic crisis, pp. 128–9.

Chronic/maintenance

- First line: azathioprine 50mg daily, increased to a maintenance dose of 2–3mg/kg at 2- to 4-weekly intervals.
- Second line: mycophenolate mofetil 500mg bd, increased to 1g bd after 4 weeks, or methotrexate.
- Third line: rituximab, calcineurin inhibitors (ciclosporin, tacrolimus), or cyclophosphamide.

Surgical

- Thymectomy.

For drugs to avoid, see Box 8.1.

Box 8.1 Drugs to avoid in myasthenia gravis

Medications exacerbating weakness in myasthenia gravis and potentially triggering a myasthenic crisis

- *Anaesthetics*:
  - depolarizing neuromuscular blockers: suxamethonium;
  - non-depolarizing neuromuscular blockers: pancuronium, etc.
- *Antiarrhythmic agents*:
  - quinidine, quinine, procainamide.
- *Antibiotics*:
  - aminoglycosides: gentamicin, amikacin, etc.;
  - quinolones: ciprofloxacin, norfloxacin;
  - tetracyclines: doxycycline, minocycline.
- *Antihypertensives*:
  - beta-blockers, calcium channel blockers.
- *Antimalarials*:
  - chloroquine.
- *Antirheumatics*:
  - chloroquine, hydroxychloroquine, penicillamine.
- *Botulinum toxin*.
- *Chemotherapy*:
  - cisplatin.
- Corticosteroids (rapid introduction or dose increase).
- *Neuropsychiatric drugs*:
  - lithium, chlorpromazine, phenytoin.

Evidence base

- *Symptomatic treatment*: pyridostigmine has not been trialled in a prospective, randomized fashion. However, in view of overwhelming clinical experience, it remains the first-line therapy. Neostigmine is occasionally used in intensive care settings. It should be noted that high doses of pyridostigmine can lead to desensitization of acetylcholine receptors, inducing muscle weakness and a cholinergic crisis, difficult to distinguish clinically from a myasthenic crisis (see details on cholinesterase inhibitors under Myasthenic crisis, Symptomatic treatment, p. 129).
- *Immunomodulation*: most patients with generalized disease will not achieve adequate response to pyridostigmine alone and require immunosuppression.
- *Induction of remission*: corticosteroids are the definitive short-term immunosuppressant therapy and are typically used as an interim measure, while long-term immunosuppressants take effect. It is recommended that prednisolone is started at a low dose on alternate days and gradually titrated upwards to avoid the 'steroid dip' in symptoms seen 4–10 days after starting high-dose prednisolone. Prednisolone produces remission or significant improvement in up to 80% of patients. Rapid short-term remission can be achieved with IVIg or PLEX in severely affected individuals or to optimize disease activity prior to surgery. The two treatments are equally efficacious, but IVIg is easier to administer.

- *Maintenance immunotherapy*: azathioprine is the first-line agent with good evidence of efficacy in RCTs, but it is very slow to work (>1 year). Very often, it is commenced concurrently with prednisolone to allow for earlier steroid tapering. There is conflicting evidence for the efficacy of mycophenolate and no high-quality published evidence for the use of methotrexate. Several case reports describe the utility of rituximab in patients with refractory MG, particularly those with MuSK-positive disease. Ciclosporin and cyclophosphamide have a strong evidence base for maintenance immunosuppression, but their use is limited to refractory cases because of severe potential side effects. Tacrolimus is a second-line steroid-sparing agent which has been shown in uncontrolled studies to induce remission in up to 85% of patients.
- *Surgery*: thymectomy is indicated in all patients with thymoma (10–15% of patients with MG). In young, fit, ACRA-positive patients with generalized disease incompletely responsive to immunotherapy thymectomy is often offered. Its role in non-thymomatous and ocular myasthenia remains unclear and is the subject of an ongoing multicentre trial. Retrospective studies suggest significant benefit in terms of remission and reduced use of immunosupressants in post-thymectomy patients. The benefits are thought to be higher in young patients, in the first 3 years of their disease, with generalised ACRA positive disease. MuSK-positive patients are not thought to benefit from this procedure.

Myasthenic crisis

This is a life-threatening neurological emergency, characterized by the development of respiratory and bulbar muscle weakness. Mortality is around 4%. Commonly, a crisis is triggered by intercurrent illness or infection, most frequently of the respiratory tract, sometimes occurring as a direct result of aspiration from undiagnosed bulbar dysfunction. Other precipitants include surgery, pregnancy, tapering of maintenance immunosuppression, emotional stress, heat, hyperthyroidism, and various medications (See Box 8.1).

Supportive management in the form of close monitoring of airway patency and respiratory function is important. Regular FVC assessments are essential, and FVCs <1–1.5L or a rapid fall in FVCs will guide the need for admission to the intensive care unit (ICU) for prompt intubation and ventilation, if required, while immunotherapy is being instituted.

Treatment

Supportive management

Patients should be admitted to the ICU early, as elective intubation and ventilation may be required. Should neuromuscular blockade be needed, succinylcholine can be used, although higher doses than normal will be necessary. Non-depolarizing neuromuscular blockers should be used with caution.

Immunomodulatory therapy

- First line: IVIg 0.4g/kg/day for 5 days or PLEX, plus prednisolone 60–80mg od.
- Second line: azathioprine and mycophenolate.

Rapidly acting immunomodulatory therapies, either IVIg or PLEX, are the preferred modalities of treatment.

Symptomatic treatment

- Cholinesterase inhibitors: IV pyridostigmine 2mg 4- to 6-hourly if intubation not required. Many units withhold cholinesterase inhibitors during acute immunomodulatory therapy due to their propensity to potentiate cholinergic crises and to increase respiratory secretions, impairing airway clearance in intubated patients.

Evidence base

A number of large prospective trials have shown no significant difference in efficacy between IVIg and PLEX for exacerbations of MG, although IVIg is more likely to be tolerated.

Corticosteroids should be started concurrently with IVIg or PLEX, as the effects of these acute therapies are not sustained beyond a few weeks. The risk of a 'steroid dip' is mitigated by simultaneous use of PLEX or IVIg. Steroid-sparing agents, typically azathioprine or mycophenolate, can be started in the acute phase if glucocorticoids are contraindicated or if maximal long-term immunomodulation is deemed important.

Lambert-Eaton myasthenic syndrome

LEMS is a rare acquired neuromuscular transmission disorder mediated by antibodies against presynaptic voltage-gated calcium channels (VGCCs) at the NMJ. It is five times commoner in males. Onset is usually over the age of 50 years, with slowly progressive proximal limb weakness, mostly affecting the lower limbs, often mimicking a myopathy, rather than MG, and typically exacerbated by prolonged exercise or hot weather. A distal, symmetrical, sensory neuropathy and autonomic symptoms of dry mouth, dry eyes, and erectile dysfunction may be prominent. Ocular and bulbar symptoms occur less frequently than in myasthenia. Respiratory involvement occurs rarely. About 50% of cases are paraneoplastic, associated with SCLC (>80%), lymphoproliferative disorders, and rarely other malignancies. Non-paraneoplastic cases are of a primary autoimmune aetiology.

Circulating P/Q type VGCC antibodies are detectable in 85% patients. In contrast to myasthenia, EMG with repetitive stimulation at 10Hz shows a characteristic increment of CMAP amplitude.

Treatment

Treatment of the underlying malignancy may cause symptom regression.

Symptomatic therapy

- First line: 3,4-DAP 15mg/day, increasing up to 60mg/day.
- Second line: pyridostigmine 60–90mg every 4–6h.

- Third line: guanidine 5–10mg/kg/day, increasing up to a maximum of 30mg/kg. Patients should be monitored for the development of bone marrow suppression.

Immunomodulatory therapy

- First line: trial of IVIg (2g/kg), acutely or as maintenance therapy, every 1–3 months.
- Second line: prednisolone 1mg/kg/day ± azathioprine (50mg bd) or mycophenolate mofetil (1g bd).
- Third line: ciclosporin, rituximab, PLEX.

Evidence base

- *Symptomatic therapy*: 3,4-DAP has been shown to improve muscle strength and resting CMAP amplitude in up to 79% of patients. Adjunctive treatment with pyridostigmine may confer additional benefit. Pyridostigmine, when combined with low-dose guanidine (<1g/day), is a safe and effective alternative.
- *Immunotherapy*: most patients with non-paraneoplastic LEMS require long-term immunosuppression, usually with steroids and azathioprine. There are no large-scale trials firmly demonstrating the magnitude of clinical improvement with oral prednisolone or azathioprine, but their use is widespread, following several case reports. Corticosteroids also appear to be of benefit in patients with LEMS due to underlying SCLC. In a randomized cross-over trial, IVIg was shown to significantly improve limb, respiratory, and bulbar muscle strength, compared to placebo. Patients with LEMS do not respond as well to PLEX as those with myasthenia, and its use is marred by a short duration of action and continued production of antibodies, particularly in paraneoplastic disease. Isolated case reports support the use of rituximab for resistant cases.

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Chapter 9

Parkinson's disease and parkinsonism

Introduction

Parkinsonism, a syndrome characterised by the presence of bradykinesia, accompanied by tremor, rigidity, and/or postural instability, has several different causes. Identifying the underlying aetiology is particularly important, as idiopathic Parkinson's disease (PD), the commonest akinetic rigid syndrome, is very amenable to therapeutic intervention. In addition to idiopathic PD and the Parkinson plus syndromes, there are several other causes of secondary parkinsonism, including drug-induced parkinsonism, Wilson's disease (WD), vascular parkinsonism, and the Westphal variant of Huntington's disease (HD).

In this chapter, we will discuss the commonest akinetic rigid syndromes and their treatment.

Parkinson's disease

PD is one of the commonest movement disorders. It has a prevalence of 160 per 100000 in the general population, higher in the elderly where it affects almost 4% of those over 80 years of age. Although initially considered to be solely a disorder of motor control, non-motor features have become increasingly recognized as important and critical to a patient's quality of life. These non-motor features include constipation, postural hypotension, neuropsychiatric disturbance (cognitive dysfunction, depression, and psychosis), and disorders of sleep.

Management of Parkinson's disease

To aid management decisions in the treatment of PD, guidance has been produced by NICE in the UK and the AAN in the USA. A comprehensive evidence-based review of the efficacy of PD treatments has also been created by the International Parkinson and Movement Disorder Society (MDS).

As a general rule, patients should be referred to a specialist for assessment and confirmation of the diagnosis prior to initiation of treatment. If confirmed, appropriate counselling should be given and advice provided regarding the risks and benefits of medication, as well as the likely natural course of the disease. A minimum of a yearly review is essential, in order to ascertain the rate of disease progression, as well as the ongoing effectiveness and side effects of medications.

Patients benefit from access to specialist nurses, as well as physiotherapists, occupational therapists, and speech and language therapists, as appropriate. For most patients, PD is a slowly progressive disease giving patients the opportunity to plan for an inevitable deterioration in their condition. This can be facilitated by referral to palliative care teams and advanced care planning with their specialist or family doctors.

Treatment of motor symptoms

Early disease

'Early disease' refers to PD in people who have only begun to develop functional disability and require symptomatic therapy.

Treatment

The decision to initiate treatment is based on clinical and lifestyle factors and the patient's preference. No particular agent has been identified as the best first choice, but dopamine agonists (DAs) and other alternatives to levodopa are often used with the hope of delaying the onset of motor complications seen with prolonged levodopa treatment. However, levodopa remains the most effective drug treatment for PD, and patients who are started on other drugs will often experience significant benefit when levodopa is started. If patients gain no benefit from levodopa or DAs, then the diagnosis of idiopathic PD should be reconsidered.

With all symptomatic treatments, the lowest effective dose of any agent should be used to avoid side effects. The following agents are used in early PD.

1. DAs:
   - non-ergot agonists are now preferred over ergot-derived agonists;
   - use an alternate agonist or a different drug class if unable to titrate to an effective tolerable dose;
   - as the disease progresses, most patients will require the addition of levodopa.
2. Levodopa:
   - it provides the greatest degree of symptom control;
   - use the lowest effective dose.
3. Monoamine oxidase B (MAO-B) inhibitors:
   - monotherapy has only modest symptomatic benefit.
4. Anticholinergics/β-blockers (typically propranolol) to alleviate tremor:
   - valuable, particularly in young patients with early PD and severe tremor. Avoid anticholinergic use in the elderly, due to greater susceptibility to confusion and other side effects.

Later disease

'Later disease' refers to people with PD on levodopa who have developed motor complications. Motor complications occur in up to 60% of patients after 5–10 years of levodopa therapy. They include motor fluctuations, 'off' periods, dyskinesias, and dystonia. Those with a younger age at onset or taking higher doses of levodopa are at higher risk of developing complications earlier.

Treatment

Adjunctive treatments that may be used with levodopa:

- DAs: see Early disease, p. 136;
- MAO-B inhibitors: see Early disease, p. 136;

- catechol-*O*-methyltransferase (COMT) inhibitors: entacapone may be used first-line, in combination with levodopa and dopa decarboxylase (DDC) inhibitors. Tolcapone can be used if entacapone is ineffective. Due to the rare risk of fulminant hepatitis, close monitoring of liver function is required.

Management of complications of therapy/progressive disease

1. Drug-induced dyskinesias.

Sixty per cent of levodopa-treated patients develop dyskinesias by 10 years of treatment. During 'on' periods, dyskinesias are commonly choreiform when mild but can be ballistic when severe. 'Off' period dyskinesias are often dystonic.

Dyskinesias often occur at peak dose (60–90min after the last levodopa dose) or may be biphasic (just before: trough; and after a dose: peak) when concentrations of levodopa are just below or above the effective range.

Treatment

- Reduce fluctuations in serum levels of levodopa by giving smaller doses more frequently. A compromise should be reached between adequate motor control and dyskinesias.
- Switching from controlled-release (CR) to immediate-release (IR) preparations of levodopa may allow easier adjustment of treatment regime, with faster onset of action and shorter half-life.
- Introduction of DAs or other dopaminergic agents, with a reduction in levodopa.
- Amantadine: may be used as an adjunct to levodopa in those with dyskinesias.

2. Increasing 'off' periods.

Almost all advanced PD patients ultimately experience worsening 'off' periods. 'Off' periods describe instances where it appears that levodopa has stopped having effect, also known as end-of-dose off periods.

Treatment

Simply increasing the overall levodopa dose may decrease the frequency and severity of 'off' periods but will increase peak dose side effects, including dyskinesias, hallucinations, and confusion. Smaller doses of levodopa administered more frequently will limit this problem to an extent.

Sustained-release levodopa preparations (e.g. Sinemet® CR) may similarly reduce fluctuations, but their use may be complicated by a lack of predictability of effect. Due to the reduced bioavailability of sustained-release levodopa, compared to IR, the dose may need to be increased by up to 30%. A sustained-release preparation given at night may be of use if patients experience poor nocturnal mobility, with difficulty turning over in bed, or 'off' periods on waking, which can be accompanied by painful dystonic posturing of the feet.

- DAs: see Early disease, p. 136.
- MAO-B inhibitors: see Early disease, p. 136.
- COMT inhibitors: see Late disease, pp. 136–7.

- Apomorphine:
  - SC injections can be very useful as rescue therapy for freezing and unpredictable 'off' periods;
  - continuous SC infusions are used in patients with severe motor fluctuations despite optimal oral therapy.

Surgical interventions

Neurosurgery

Surgical interventions have been shown in several high-quality trials to be an effective treatment for motor fluctuations and dyskinesias in advanced PD, when compared to best medical therapy.

- Surgery is indicated only in those with disabling motor fluctuations and/or dyskinesias that are unresponsive to medical therapy.
- The main targets for DBS are the subthalamic nucleus (STN) or the globus pallidus (GPi).
- STN DBS allows for greater reduction in medication but may be associated with worsening of non-motor symptoms and falls.
- All levodopa-responsive symptoms, except for axial symptoms (such as freezing of gait and falls), respond to DBS.
- Thalamic stimulation may be valuable in patients with severe tremor.
- The EARLYSTIM trial of STN DBS found significantly improved quality of life at 2 years in patients with early motor complications, compared to those treated with best medical therapy alone. This study has highlighted a possible role for DBS earlier in the disease course of PD.

Enterally administered levodopa/carbidopa gel (Duodopa®)

Duodopa® is a levodopa-based gel administered via percutaneous endoscopic gastrostomy (PEG) or jejunostomy (PEJ). It provides continuous intestinal infusion of levodopa, thereby avoiding fluctuations in absorption that are due to delayed gastric emptying and diet-related competition for intestinal uptake in advanced PD. It is considered after failed medical treatment for motor complications. Trials have suggested that it reduces the rate and severity of levodopa-related motor complications and improves quality of life. The MDS evidence-based review supported its use in the treatment of motor fluctuations and dyskinesia. However, stronger evidence is required to label the treatment as clearly efficacious.

Non-motor symptoms

Autonomic disturbance

Autonomic disturbance occurs early in PD. Dysfunction spans the sympathetic, parasympathetic, and enteric nervous systems. Common symptoms include constipation, sialorrhoea (drooling), postural hypotension, urinary urgency and urge incontinence, hyperhidrosis, and sexual dysfunction.

Treatment

- Postural hypotension:
  - conservative measures: increased dietary salt, adequate fluid intake, and compression stockings;
  - fludrocortisone;
  - midodrine.
- Constipation:
  - dietary advice;
  - macrogol (e.g. Movicol®).
- Sexual dysfunction:
  - sildenafil.
- Sialorrhoea:
  - glycopyrronium bromide;
  - hyoscine hydrobromide;
  - botulinum toxin A (BTX-A);
  - botulinum toxin B (BTX-B).

Evidence base

1. Fludrocortisone and midodrine (see drug monographs Fludrocortisone, pp. 465–6, and Midodrine, pp. 526–8).
2. Macrogol has been assessed in one RCT in PD patients (n = 57). There was a significant improvement in constipation in the macrogol grouped, compared to placebo.
3. Sildenafil was assessed in one randomized, double-blind cross-over study for safety and efficacy in erectile dysfunction related to PD. Subjects (n = 10) treated with 25–100mg of sildenafil 1h prior to sexual intercourse showed significant improvements in the ability to achieve and maintain an erection, compared to placebo.
4. Glycopyrronium bromide (1mg bd for 1 week) was assessed in a randomized, double-blind, placebo-controlled trial for drooling in PD (n = 23). It achieved >30% decrease in sialorrhoea score, compared to placebo. There have been no trials of hyoscine hydrobromide in PD-related sialorrhoea. However, small, short-term studies have shown it to be effective. It is available as a transdermal patch and tablet.
5. BTX-A (50 units in each parotid gland) was assessed in a double-blind, randomized, placebo-controlled trial over 1 month (n = 32). BTX-B (each parotid gland received 1000 units of BTX-B, and each submandibular gland 250 units of BTX-B) was assessed in a 4-week, double-blind, randomized, placebo-controlled, parallel-group

study (n = 16). Both significantly reduced drooling. Dysphagia due to diffusion into nearby muscles was experienced as a side effect; however, often there was no difference from placebo. It should be noted that only patients with mild or no dysphagia were included in studies.

Parkinson's disease dementia

PD dementia (PDD) occurs in up to 40% of patients during the course of the disease. Executive dysfunction, and visuoperceptive and visuoconstructive deficits are prominent features, with relative preservation of memory, compared to Alzheimer's dementia. Visual hallucinations occurring earlier in the course of PD increase the risk of developing cognitive dysfunction. Importantly, dementia developing before, concurrent with, or shortly after the onset of parkinsonism suggests dementia with Lewy bodies (DLB), rather than PDD.

PDD and its management are discussed further in Chapter 11, Dementia.

Depression

Depression is present in up to 50% of PD patients. 'Off' period-related depression has also been described; it is important to differentiate this from global depression, as this will generally respond to dopamine replacement.

Treatment

No clear first-line agent has been identified to treat depression in PD. Frequently used agents include:

- SSRI (fluoxetine, sertraline, citalopram, and paroxetine);
- TCA (nortriptyline, desipramine, and amitriptyline);
- DAs (pramipexole and ropinirole).

Evidence base

SSRIs are often used first-line, as they have a better side effect profile, avoiding the anticholinergic and pro-arrhythmogenic effects associated with TCAs. However, in patients with significant tremor and no cognitive deficit, the anticholinergic activity of TCAs may result in improvements in tremor, alongside improvement in mood.

Selective serotonin reuptake inhibitors

Several small RCTs have assessed the efficacy of SSRIs in the management of PD-associated depression, with varying results. Citalopram, sertraline, paroxetine, and fluoxetine were reviewed in the most recent MDS evidence-based review, which concluded that there was an absence of strong evidence demonstrating efficacy of these agents. However, overall use was supported, and it does not require specialized monitoring.

Cautions with SSRIs:

1. a small body of literature has highlighted the rare occurrence of worsening motor symptoms with SSRIs (most notably with fluoxetine and paroxetine). Therefore, introduction of these agents should be undertaken cautiously, with regular review of motor symptoms;

2. combinations of SSRIs and MAO-B inhibitors pose the theoretical risk of serotonin syndrome. Caution should be taken if using both agents together (see drug monograph Monoamine oxidase inhibitors, pp. 314–17).

Dopamine agonists

A double-blind, placebo-controlled RCT (n = 287) of pramipexole (0.125–1.0mg tds) showed a significant reduction in Beck Depression Inventory (BDI) scores, compared to placebo. The MDS evidence-based review concluded that pramipexole was efficacious and clinically useful in the treatment of PD-related depression. Ropinirole has not been assessed by means of an RCT for this indication; however, a prospective cohort study (n = 44) showed significant improvement in depression and anxiety scores after 6 months.

Psychosis

A study of 230 patients with PD found that 60% of patients exhibited features of psychosis, particularly visual hallucinations, over the study period. Risk factors include older age at onset, need for high doses of dopaminergic drugs, and REM sleep behaviour disorder.

Treatment

1. Review medications: a reduction in antiparkinsonian therapy may alleviate psychotic symptoms. Anticholinergics, amantadine, COMT inhibitors, and DAs may be discontinued or reduced, in this order, reflecting the relative likelihood of each agent causing or exacerbating psychosis. Levodopa dose reduction can also be considered as a last resort.
2. Antipsychotics: typical antipsychotics commonly aggravate motor symptoms in PD, because of their antidopaminergic activity. For this reason, atypical antipsychotics are preferred:
   - first line: quetiapine;
   - second line: clozapine.

Evidence base

Although the available evidence for clozapine (several double-blind controlled trials) is stronger than for quetiapine (conflicting results from open-label and double-blind, placebo-controlled trials), quetiapine is often used in preference because of its more favourable side effect profile.

Sleep disturbance

Excessive daytime sleepiness is a common non-motor feature of PD, affecting 51% of patients in one study. It may result from the disease process itself or as a consequence of dopaminergic therapy. Sudden-onset sleep or 'sleep attacks' are an infrequent, but important, side effect of dopaminergic therapy (particularly DAs; see drug monographs Ergot-based dopamine agonists, pp. 310–13, and Non-ergot-based dopamine agonists, pp. 318–22). Both somnolence and sudden onset of sleep will impair the patient's quality of life and impact on their ability to drive.

Treatment

1. Lifestyle interventions: assess sleep hygiene, and provide advice to ensure adequate sleep.
2. Modafinil.

Evidence base

Three small RCTs have investigated the use of modafinil (200–400mg/day) for excessive daytime sleepiness in PD. Only one showed a significant difference from placebo. No long-term efficacy or safety data are available, as no study lasted >4 weeks. The MDS evidence-based review emphasizes that modafinil for this indication remains under review and that larger, high-quality studies are needed.

Parkinsonism plus syndromes

Multisystem atrophy

Multisystem atrophy (MSA) is a rare neurodegenerative disorder, characterized by the combination of parkinsonism, dysautonomia, cerebellar dysfunction, and corticospinal degeneration. It has been estimated to occur in 3 in 100000 people aged over 50, with an average age of onset of 56. Both men and women are affected equally. Symmetrical extrapyramidal signs and rapid deterioration of mobility with early falls help distinguish it from idiopathic PD. Diagnosis is based on clinical findings and poor response to levodopa, and supported by neuro-imaging, such as abnormal DaTscan and characteristic MRI findings, although the latter are often normal in early disease.

Treatment

There are no curative or disease-modifying treatments for MSA. Therapy is symptomatic.

1. Parkinsonism:
   - first line: a trial of levodopa (up to 1000mg/day for 3 months). This will also help differentiate MSA from idiopathic PD. Classically, MSA is resistant to dopaminergic therapy, although 30% of patients may experience a transient improvement. Worsening postural hypotension, dyskinesias (in particular facial or cervical dystonia), nausea, and vomiting may limit its use.
   - second line: amantadine and DAs are sometimes used.
2. Autonomic dysfunction:
   - postural hypotension: drug therapy is used, in addition to conservative measures, ensuring adequate salt and water intake, review of medications, and elastic stockings:
     — first line: fludrocortisone;
     — second line: midodrine.
   - overactive bladder (OAB):
     — first line: muscarinic acetylcholine receptor (AChR) antagonists (e.g. oxybutynin or tolterodine);
   - erectile dysfunction:
     — first line: sildenafil.

Evidence base

1. Levodopa: there are no controlled trials of levodopa for the treatment of MSA. Case series suggest ~30% of patients exhibit some benefit with levodopa therapy. This benefit is rarely sustained, and most patients experience deterioration in their symptoms after a few years. Some patients report subjective benefit following levodopa therapy, without objective improvement in motor examination. Levodopa is less likely to cause psychiatric side effects and motor fluctuations in MSA than in PD, but dyskinesias may still occur without improvement in parkinsonism.

2. DAs: there have been no controlled trials of DAs in MSA. Due to their increased side effect profile, compared to levodopa, they are not generally used. A double-blind, placebo-controlled trial showed no benefit of amantadine in MSA. However, 5% of patients in an older series showed a 'good or excellent response', as rated by subjective assessment of the patient or their family or clinician.
3. Alternative agents: the use of SSRIs in MSA has also been investigated. A double-blind, placebo-controlled trial investigated the use of paroxetine (30mg tds for 2 weeks) and concluded that there was a small, but statistically significant, improvement in motor symptoms during treatment.

Progressive supranuclear palsy

Progressive supranuclear palsy (PSP) is the commonest of the atypical parkinsonian syndromes, affecting up to 6.4 per 100 000 people, with an average age of onset at 62 years. Patients exhibit early gait disturbance with falls and significant axial rigidity, dysarthria, pseudobulbar palsy, and a characteristic eye movement abnormality (initially slowing of vertical > horizontal saccadic velocities, with later complete supranuclear gaze palsy). Insomnia and frontal cognitive abnormalities are common, but REM sleep behaviour disorder (RBD) is not.

Treatment

There are no curative or disease-modifying treatments for PSP. Therapies are symptomatic. As with other atypical parkinsonian syndromes, PSP is generally not responsive to levodopa, although a proportion of patients experience transient benefit.

- First line: levodopa trial (up to 1000mg/day for 3 months).
- Second line: amantadine.

Evidence base

There is a lack of clinical trial evidence of efficacy of levodopa in PSP. Small retrospective series have reported temporary benefit in up to 54% of patients, with doses as high as 9000mg/day. 'Modest improvement' was noted in four out of 12 patients in a series of post-mortem confirmed cases. Visual hallucinations are a common side effect of levodopa use in PSP. There is a lack of clinical trial evidence for the efficacy of amantadine in PSP. Small retrospective series have noted transient therapeutic benefit in up to 29% of patients.

Corticobasal degeneration

Corticobasal degeneration (CBD) describes a progressive neurodegenerative disorder, characterized by asymmetrical onset of rigidity, apraxia, tremor, stimulus-sensitive myoclonus, and dystonia. Patients often complain of symptoms initially affecting one limb and may experience the alien limb phenomenon. Sensory symptoms are common, including significant pain. Cognitive and behavioural abnormalities are an important feature and often precede motor symptoms. The condition has been estimated to occur in 5–7 in 100 000 and has an average age of onset of 63.

Treatment

There are no curative or disease-modifying treatments for CBD. Management is with symptomatic treatment.

- Parkinsonism:
  - first line: trial of levodopa (up to 1000mg/day for 3 months). Lack of response or a short-lived response is typical.
- Myoclonus:
  - clonazepam, sodium valproate, piracetam, or levetiracetam.

Evidence base

There are no RCTs investigating the efficacy of treatments used in CBD. Small retrospective case series note transient mild to moderate improvement in parkinsonism with levodopa. Dyskinesias are a reported side effect.

Dementia with Lewy bodies

DLB is a syndrome characterized by a triad of fluctuating cognition, recurrent visual hallucinations, and spontaneous motor features of parkinsonism. Dementia must precede or accompany the spontaneous onset of parkinsonism, to differentiate this disease entity from PDD which manifests >1 year after the typical motor symptoms of PD.

DLB and its management are discussed further in Chapter 11, Dementia.

Drugs to avoid in parkinsonism

A number of medications used in everyday clinical practice have the potential to worsen the symptoms of PD.

Drug-induced parkinsonism is the second commonest cause of an akinetic rigid syndrome and is often the result of treatment with antidopaminergic medications (e.g. antipsychotics, antiemetics). Classically, drug-induced parkinsonism is thought to be reversible on stopping the offending agent. However, up to 10% of patients develop persistent or progressive parkinsonism. A review of medications in all patients presenting with parkinsonism is important to ensure causative or exacerbating agents are stopped.

Below is a list of commonly used antidopaminergic agents which should be avoided or used with caution in patients with PD. For pharmacokinetic and further pharmacodynamic interactions of drug treatment, see individual drug monographs.

Antidopaminergic agents include:

- antiemetics:
  - metoclopramide;
  - prochlorperazine.
- antihistamines:
  - promethazine;
  - alimemazine.
- antipsychotics:
  - chlorpromazine;
  - clozapine;*
  - flupentixol;
  - fluphenazine;
  - haloperidol;
  - olanzapine;*
  - pericyazine;
  - pimozide;
  - quetiapine;*
  - risperidone;
  - thioridazine;
  - tiotixene;
  - trifluoperazine;
  - zuclopenthixol.
- dopamine degradation:
  - tetrabenazine.

* Medications frequently used in PD patients.

Impulse control disorders

Impulse control disorders (ICDs) are common in PD. They are pathological behaviours thought to be the result of altered reward or incentive mechanisms, likened to addiction. The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) describes ICDs as '*a group of psychiatric disorders characterised by a failure to resist an impulse, drive or temptation to perform an act that is harmful to the individual or to others*'. They are associated with dopaminergic treatment, particularly DAs.

Management of impulse control disorders

Recognition of ICDs is often difficult, due to a patient's lack of insight into pathological behaviours and their association with dopaminergic therapy. Patients and families should be made aware of common ICDs and advised to alert their physician of possible symptom onset. Due to embarrassment, patients may not be forthcoming about ICD-related activities, and hence these need to be discussed actively.

Following diagnosis, management should be undertaken in a multidisciplinary setting, with involvement of a PD nurse specialist and psychological support services.

- Patients with ICDs should have their dopaminergic replacement therapy (DRT) gradually reduced, with close monitoring of motor performance. Withdrawal symptoms may be noted if dose reduction is too abrupt.
- Where possible, DA should be discontinued, and levodopa or alternative therapies, e.g. DBS, used in its place.
- For some patients, changing dopaminergic agonists may be effective. As explained above, those with higher D3 receptor affinity should theoretically be more likely to induce ICDs (e.g. pramipexole > ropinirole). However, any difference clinically between these two agents was not apparent in the DOMINION study.
- Other agents which may be effective include:
  1. antidepressants (e.g. SSRIs) for pathological gambling;
  2. atypical antipsychotics (e.g. quetiapine, clozapine).

Evidence base

1. There have been very few robust studies on pharmacological treatment of ICDs in PD. Case reports and case series have reported improvement in ICDs following reduction and/or discontinuation of DA therapy, with suggestion of improvement in some patients when switching from agents with relatively high D3 affinity.
2. Treatment of pathological gambling with SSRIs, including fluvoxamine ($n = 10$) and paroxetine ($n = 45$), has been assessed in small RCTs. Short-term benefits were shown by both agents, compared to placebo. It should be noted that these studies were not specific for PD-related ICDs.
3. Case reports have suggested a role for atypical antipsychotic treatment in cases of hypersexuality.
4. DBS has been used to treat ICDs, with conflicting results. The STN was the most reported target of lead placement. Often, improvements could not solely be ascribed to surgical intervention, due to confounding reduction in DRT post-operatively.

Dopamine agonist withdrawal syndrome

Dopamine agonist withdrawal syndrome (DAWS) is a constellation of autonomic and neuropsychiatric symptoms that can occur following reduction and discontinuation of DA treatment. Autonomic symptoms include postural dizziness and sweating, and neuropsychiatric symptoms include depression, anxiety, fatigue, and insomnia.

Management of dopamine agonist withdrawal syndrome

Management of DAWS is through gradual reduction of DA, early recognition, and substitution of alternative dopaminergic therapy where necessary. There are several case reports describing successful use of off-licence drugs (e.g. apomorphine). Published series indicate that DAWS resolves within 6 months in the majority of cases. In a small proportion of patients, the DA cannot be completely discontinued. Patients and carers should be informed about the possibility of DAWS prior to commencement of DA treatment.

Evidence base

There are no RCTs investigating the management of this condition; thus, treatment recommendations are based on case reports and expert consensus.

Serotonin syndrome

Serotonin syndrome is a potentially fatal condition which results from excess serotonergic activity. It may occur either through overdose of serotonergic drugs, administration of two or more drugs with serotonergic activity, or co-administration of a drug which acts to elevate plasma levels of serotonergic drugs or serotonin directly. Onset of symptoms and signs most often occurs within 24h of changes in medication.

The commonest offending medications are SSRIs. Other offending agents include: analgesics such as fentanyl and tramadol, TCAs, MAOIs, SNRIs, triptans, lithium, linezolid, carbamazepine, valproate, herbal supplements including St John's wort, ginseng, methylphenidate, and illicit drugs including LSD, cocaine, ecstacy, and amphetamines.

At toxic levels of serotonergic activity, a triad of changes may occur:

1. changes in mental status, e.g. agitation and confusion;
2. autonomic hyperactivity, e.g. diaphoresis, diarrhoea, dilated pupils, and hyperthermia, as well as changes in heart rate and BP;
3. neuromuscular abnormalities, e.g. clonus, tremor, hyperreflexia, and muscle rigidity, occur.

Not all features need to be present to make the diagnosis.

Management of serotonin syndrome

1. Stop offending medication(s).
2. Supportive management: aim to correct abnormal vital signs (e.g. with IV fluids and cooling).
3. Benzodiazepines, e.g. diazepam or lorazepam, for myoclonus and agitation.
4. Cyproheptadine may be used in moderate to severe cases (5HT2A antagonist). The initial dose is 12mg, followed by 2mg every 2h, or 4–8mg every 6h, if the patient remains symptomatic.

Most patients improve within 24h of stopping the offending agents. Severe cases should be managed in an intensive care setting.

Evidence base

There are no RCTs investigating the management of this condition; thus, treatment recommendations are based on expert consensus.

Neuroleptic malignant syndrome/ Parkinson's hyperpyrexia syndrome

Neuroleptic malignant syndrome (NMS) is a life-threatening neurological emergency. NMS or an NMS-like syndrome may develop in the setting of PD, in relation to the use of antidopaminergic agents, or with dose reduction, treatment withdrawal, or change in dopaminergic agent. Here, the term Parkinson's hyperpyrexia syndrome (PHS) is often used. The syndrome consists of fever, rigidity, change in mental status and dysautonomia in the form of fluctuating BP, tachycardia, sweating, and urinary incontinence.

Management of neuroleptic malignant syndrome/ Parkinson's hyperpyrexia syndrome

Treatment

Management is primarily supportive, aiming to reverse any changes in dopaminergic drugs, including terminating the use of antidopaminergics where possible, and to prevent complications such as aspiration pneumonia and renal failure.

In moderate to severe cases, dopaminergic agents can be added:

- bromocriptine: 2.5mg every 6–8h PO or via nasogastric tube, then titrated over 48h up to 30–40mg/day.
- apomorphine: if PO administration is not possible, SC apomorphine may effective as an alternative.

Muscle relaxants are used for severe rigidity:

- dantrolene: 25mg every 8h PO or 1–2.5mg/kg IV (can be repeated to a maximum dose of 10mg/kg/day).

Severely ill patients may require intubation and ventilation in an intensive care setting.

Evidence base

There are no RCTs investigating the management of NMS/PHS, and treatment recommendations are based on published reports and expert consensus.

Prognosis

Most cases resolve within 2 weeks, with little residual deficit. Poorer outcomes are noted in those with complicating renal failure or a background history of drug or alcohol abuse. The clinician needs to be aware that patients with NMS are at risk of arrhythmia, aspiration pneumonia, metabolic abnormalities, respiratory failure, rhabdomyolysis, physical injuries, and VTE. Prolonged periods of severe hypoxia or hyperthermia may also result in persistent neurological disability.

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Chapter 10

Hyperkinetic movement disorders

Introduction

Hyperkinetic movement disorders are those in which there is an excess of involuntary movement. They can be classified by the clinical phenomenology and include ataxia, chorea, dystonia, myoclonus, restless legs syndrome, tics, and tremor. Treatment options have grown rapidly in number, and there are now a wide variety of both pharmacological and neurosurgical approaches to long-term management of these conditions. This chapter will discuss the clinical features, management, and evidence base for the treatment of the various hyperkinetic movements, focusing on those amenable to symptomatic treatment. Each hyperkinetic movement may have multiple aetiologies; we have emphasized notable causes (e.g. essential tremor, dopa-responsive dystonia) where significant evidence exists for their treatment.

Tremor

Tremor is diagnosed based on the presence of rhythmic and oscillatory movements of a body part. Tremors can be divided by the presence or absence of characteristic features, including whether they occur at rest (e.g. parkinsonian tremor) or on action (postural, kinetic, and intention tremors).

1. *Resting tremor*: this is most often seen with PD and parkinsonism. It is present at rest, is terminated on action, and most commonly affects the arms, legs, and chin.
2. *Postural tremor*: this tremor occurs when a body part is used to maintain a position against gravity. The underlying cause may be enhanced physiological tremor, essential tremor (ET), dystonic tremor, or PD. It most often affects the arms, head, and neck.
   - Enhanced physiological tremor has a frequency of 8–12Hz. Causes may be broadly classified into those due to hormones (stress, anxiety, thyrotoxicosis, phaeochromocytoma, and hypoglycaemia), drugs (e.g. β2-adrenergic agonists, sympathomimetics, lithium, and sodium valproate), and toxins (e.g. alcohol and benzodiazepine withdrawal, caffeine, mercury, and lead).
3. *Kinetic tremor*: this tremor is present upon movement of a body part. The commonest cause is ET.
4. *Intention tremor*: this tremor arises on moving a body part (most commonly the arms) towards a target. The amplitude of the tremor will increase, as the body part nears its target. It is often a sign of cerebellar pathology but may also be present in ET.

The effect of tremor on function will depend upon its amplitude and the limbs involved. Treatment options depend on the type of tremor, the likely underlying pathophysiology, the level of functional disability, and the patient's tolerance to medication.

Essential tremor

ET is characterized by an 8–10Hz tremor, which commonly affects the hands and arms, and may be asymmetrical at onset. Males and females are equally affected. Alcohol consumption can often lead to transient resolution of ET, with rebound worsening of tremor described when the effects wear off. Those that receive treatment often struggle with the side effects of commonly used agents.

Treatment

- First line: propranolol.
- Second line: primidone.
- Third line: gabapentin or topiramate.
- Other: benzodiazepines (e.g. clonazepam), zonisamide, levetiracetam, or botulinum toxin.
- Surgical: DBS or ablation of the ventral intermediate (VIM) nucleus of the thalamus, contralateral to the most severely affected limb. Bilateral thalamotomy is not performed, due to the high risk of speech disturbance and other side effects.

Evidence base

Propranolol and primidone have the strongest evidence base for use in the management of ET. Multiple RCTs have demonstrated their effectiveness. Both agents reduce tremor by 50%, as measured by accelerometry. As a result, the AAN has given both these agents the highest level of recommendation of efficacy. Primidone is usually used second-line to β-blockers, due to its broader side effect profile—sedation and vomiting are the commonest dose-limiting side effects, although depression, as well as cognitive and behavioural disturbances typical of barbiturates, can also be a problem. If patients have a history of asthma or experience bronchospasm with propranolol, a selective β1-adrenergic receptor blocker is preferred such as atenolol. RCTs, including comparative studies with propranolol, have shown that atenolol is effective in the management of ET, but there is no evidence that it is more effective than propranolol. Sotalol, nadolol, and metoprolol have also demonstrated efficacy in RCTs.

Alternative treatments include the anticonvulsants gabapentin and topiramate, which have demonstrated efficacy in small RCTs. RCTs of botulinum toxin had varying results. These trials have shown that, when wrist extensors and flexors are treated, a 57–68% improvement in postural hand tremor can be expected; however, arm weakness occurred in >90%. The lack of strong evidence and the occurrence of arm weakness mean that botulinum toxin is rarely used for this indication.

Holmes' tremor

The Holmes' or rubral tremor is classically associated with a lesion of the red nucleus and most often seen with ischaemic or inflammatory (e.g. MS) lesions. The tremor is typically low frequency (3–5Hz) and may have rest, intention, and postural components. Other signs of brainstem involvement are usually present, including eye movement abnormalities, hemiparesis, and ataxia.

Treatment

Brainstem tremors may be very disabling and respond poorly to pharmacological treatment. There is only case series-level evidence for the use of common pharmacological agents (e.g. trihexyphenidyl, primidone, propranolol, and levodopa). Surgical treatments have gained popularity, with thalamotomy and DBS of the contralateral nucleus ventralis intermedius (Vim) showing positive results in small series. Tremor suppression in MS occurred in 94% ($n = 161$) and 96% ($n = 97$) of patients treated with thalamotomy or DBS, respectively, in one systematic review. However, the overall contribution of tremor to functional impairment may be minimal, as most patients did not find functional improvement with successful tremor suppression. It was noted that ataxia may be worsened by surgical intervention. Due to the reversibility and ability to adjust stimulation with symptom severity, DBS is preferred; yet robust comparative evidence between surgical techniques is lacking.

Dystonia

Dystonia is characterized by sustained muscle contraction of one or more muscle groups, resulting in abnormal posturing, with or without abnormal movements of the affected limbs. It can be classified based on aetiology, age at onset, and by the areas of the body affected (focal: one body part; segmental: at least two adjoining body parts; multifocal: at least two non-contiguous body parts; hemidystonia: unilateral arm, leg, and face involvement; and generalized: involving the trunk and two other limbs). Additional features include '*gestes antagonistes*' or a 'sensory trick' whereby touching an affected body part may result in temporary resolution of the symptoms.

Treatment

The treatment of dystonias is predominantly symptomatic, with medications aimed at promoting muscle relaxation. Only rarely are drugs used which target the underlying condition, e.g. dopa-responsive dystonia (DRD). Pharmacological treatments can be divided into two main groups.

1. Botulinum toxin can provide significant symptom relief in isolated muscle groups and is very effective in focal forms of dystonia or generalized forms where symptoms from one or a few muscle groups predominate.
2. Systemic treatments may be required in more widespread forms of the condition or instances where botulinum toxin is either ineffective or not tolerated in the treatment of focal dystonia. Due to the nature of these treatments and their potential for systemic side effects, trials of treatment should be used to establish which therapies can provide maximal symptom relief, with minimal adverse effects.

In addition to drug treatment, physiotherapy is invaluable. Targeted ablation and DBS are also becoming increasingly popular. They are highly effective, even in dystonias refractory to pharmacological interventions, and often mean that systemic treatments for dystonia can be stopped or significantly reduced, avoiding or minimizing their potential side effects.

Focal

Focal dystonia affects one body part and is more commonly seen in adults. The commonest focal dystonia is cervical dystonia, e.g. torticollis; other forms include blepharospasm, limb dystonia, and task-specific dystonia.

Treatment

Botulinum toxin, unless large muscles are involved (e.g. lower limb).

- First line: botulinum toxin.
- Second line: oral agents (see Generalized, p. 158).

Evidence base

Botulinum toxin is highly effective in the management of focal dystonias. An estimated 90% of patients with blepharospasm will demonstrate clear symptomatic improvement with treatment. Further RCTs have also confirmed significant improvements when used in the management of cervical, oromandibular, limb, and laryngeal dystonias.

Generalized

Generalized dystonias encompass a wide group of conditions, with a diverse aetiology, including genetic disorders, brain injury (e.g. at birth or stroke), infection, drug-related, or idiopathic (often believed to be a genetic condition where a mutation has not yet been found). Early-onset generalized dystonias usually present in late childhood, often beginning as a focal limb dystonia and then generalizing. Primary generalized dystonia is often caused by a mutation in the *DYT1* gene. Where a definitive aetiology has not been identified in early-onset dystonia, a diagnostic trial of levodopa should be undertaken (see Dopa-responsive dystonia, p. 159).

Treatment

Oral medication is often preferred to botulinum toxin. A combination of agents may be required for optimum symptom control.

- First line:
  - diagnostic levodopa trial (DRD);
  - trihexyphenidyl.
- Second line/adjuncts:
  - baclofen (PO/intrathecal) (may be used as monotherapy, as tolerated better in the elderly than trihexyphenidyl);
  - benzodiazepines (e.g. clonazepam);
  - botulinum toxin if symptoms from one or a few muscles predominate;
  - triple therapy with an anticholinergic, tetrabenazine, and a dopamine antagonist (atypical antipsychotics such as clozapine) may be beneficial in severe generalized dystonia.
- Surgery: localized ablation or DBS.

Evidence base

- Due to the variable presentation of DRD, a trial of levodopa for 4 weeks is often undertaken. Following this, symptomatic treatment may be started with trihexyphenidyl, the anticholinergic with the greatest evidence for the treatment of dystonia. Sustained benefit was noted after 2 years in 41% of patients treated in one RCT. PO baclofen may improve dystonia-related gait disorder, with intrathecal preparations being of benefit for significant lower limb spasticity. In cases of myoclonus dystonia, additional clonazepam may be helpful.
- *Surgery*: surgical options can be broadly categorized into lesional surgery (pallidotomy and thalamotomy) and DBS. Due to the permanent nature of its potential side effects, lesional therapy is now less commonly used and reserved for instances where DBS is not suitable or where prior use has resulted in complications. It is used where there is a lack of sufficient response to oral agents or botulinum toxin, particularly in those with primary dystonia. The globus pallidus internus (GPi) has been shown to be the optimal target for lead placement. The results from RCTs suggest improvement can be expected in 40–60%.

Dopa-responsive dystonia

DRD is a rare childhood-onset progressive dystonic syndrome, which shows a significant response to low-dose levodopa treatment. Symptoms usually begin in the legs and become generalized, with many later developing parkinsonism. Often symptoms are improved after sleep. DRD may also rarely present in adulthood, and this can be with parkinsonism before dystonia.

Treatment

- First line: levodopa.

Evidence base

The characteristic feature of DRD is the dramatic and sustained effect of low-dose levodopa treatment. Several series have highlighted that most DRD patients usually require around 300mg/day of levodopa. Rarely, doses from 600 to 1000mg/day are required. Patients have been shown to be stable on low-dose levodopa for up to 22 years. Motor complications, as seen with levodopa treatment in PD, do not occur in DRD. Those who developed 'wearing off' phenomena or dyskinesias may represent childhood-onset parkinsonism.

Tics and Tourette's syndrome

Tics are sudden, brief, 'involuntary' movements (motor tics) or vocalizations (phonic tics). An important distinction between tics and the other hyperkinetic movements (e.g. myoclonus and dystonia) is the ability of patients to suppress them, during which time patients often describe a rising urge or an internal unrest. This may be followed by a rebound exaggeration of their tics.

Tourette's syndrome

Tourette's syndrome (TS) is a chronic neurodevelopmental disorder, characterized by the presence of:

1. multiple motor and one or more vocal tics;
2. onset before the age of 18;
3. tics for at least 1 year.

The decision to commence treatment of tics or TS should be made based on the degree to which manifestations of these conditions intrude into a patient's life. Severe tics describe those that result in self-injurious behaviour, affect academic performance, or result in bullying. Patients and their families should be counselled on the realistic outcomes of treatment and the potential side effects of medications. Often mild tics do not require pharmacological treatment, and reassurance may be all that is required. If treatment is considered, psychological support and behavioural therapy should be offered, alongside medications.

Treatment

Tics (mild to moderate)

- First line: α2-adrenergic agonists (clonidine or guanfacine).
- Second line: antipsychotics (atypical: aripiprazole or risperidone; typical: haloperidol, pimozide, or sulpiride).
- Third line: tetrabenazine.
- Other: benzodiazepines (e.g. clonazepam) or topiramate (particularly if there is co-morbid obesity)

Tics (moderate to severe)

- First line: antipsychotics (as above).
- Adjunct: botulinum toxin (focal motor or simple vocal tics).
- Surgical: DBS and brain lesion surgery for serious cases.

Evidence base

A meta-analysis of RCTs established that antipsychotics are the most effective agents for the management of tic disorders—the standardized mean difference (SMD), compared to placebo, is 0.58 (95% CI 0.36–0.80). However, due to their side effect profile (extrapyramidal symptoms and weight gain), they are reserved for those with moderate to severe tics. Studies investigating the use of $\alpha 2$-agonists suggest that patients with co-morbid attention-deficit/hyperactivity disorder (ADHD) are most likely to benefit from treatment, as trials that excluded patients with ADHD demonstrated only a small, non-significant benefit. Clonazepam has only been trialled in open-label studies in adults where it has shown some benefits in the treatment of tics. Due to development of tolerance, sedation, and memory problems, there is limited long-term use of these agents. A survey conducted by the European Society for the Study of Tourette Syndrome found risperidone, clonidine, aripiprazole, pimozide, and sulpiride are the agents most preferred by experts.

Chorea, ballism, and athetosis

Chorea is a disorder characterized by involuntary, irregular, and random movements that appear to flow from one muscle to the next. It may affect any body part but is most commonly generalized. Ballism is more explosive and proximal in nature. When affecting one side, it is termed hemiballism or hemiballismus, and is traditionally associated with, but not limited to, a lesion of the contralateral STN. Athetosis often accompanies chorea and is a slower writhing and twisting movement that presents distally.

Treatment

In some cases, the underlying disorder may be treated (e.g. SLE, rheumatic fever, thyrotoxicosis, polycythaemia), however often treatment is aimed at symptom relief through reduction in central dopaminergic activity. Often patients are unaware of the extent or the presence of athetosis or chorea. Indications to start treatment may include physical injury, gait instability, interference with daily activities, stigma, and sleep disturbance. Medication trials should be undertaken to achieve best symptomatic control with minimal side effects. In addition to pharmacological treatment of the movement disorder, co-morbid psychiatric and psychological illness should be addressed.

- First line: amantadine or tetrabenazine.
- Second line: atypical antipsychotics (e.g. olanzapine, risperidone, and sulpiride) or typical antipsychotics (e.g. haloperidol).
- Surgical: DBS.

Evidence base

The evidence base for the pharmacological treatment of chorea is largely based on studies in HD (see Huntington's disease, pp. 162–3). Evidence for DBS treatment is from small case series which suggest benefit. However, further work is required to establish if these findings are accurate and which patients are likely to derive most benefit from this form of treatment.

Huntington's disease

HD is the commonest cause of inherited chorea, which manifests as dementia, psychiatric disturbance, and a mixed movement disorder (dystonia, parkinsonism, and chorea).

Treatment

- First line: tetrabenazine or antipsychotics.
- Second line: amantadine or riluzole.

Management of mood and behavioural disturbances that commonly occur is important. Treatment is with antidepressants, antipsychotics, and anxiolytics, in addition to counselling. Patients and their carers should be offered psychological support. Care by a specialist multidisciplinary team, where available, can help at all stages of the disease. Social isolation and motor disability are both indications for treatment.

Evidence base

Tetrabenazine will reduce chorea in ~80% of HD patients. It is the only drug that has been approved in the UK or USA for HD-related chorea.

Parkinsonism (commoner at high doses >100mg), drowsiness, and depression (which can be severe and associated with suicidal ideation) are important and common side effects (present in over 80% in some studies). They are reversible with treatment withdrawal. Active psychiatric disease or depression are a contraindication for use. Here an atypical antipsychotic, such as risperidone, olanzapine, or clozapine, may be more appropriate. Classical antipsychotics, such as haloperidol, are also effective but are associated with an increased risk of extrapyramidal side effects and should not be used first-line. The AAN states that there is 'insufficient evidence to give formal guidance on the use of antipsychotics in HD', but the combination of behavioural disorder and chorea make them a reasonable treatment choice.

RCTs investigating the use of amantadine and riluzole for HD-related chorea have failed to demonstrate clear beneficial effects. Small RCTs have suggested that riluzole (50mg bd) can provide a mild to moderate reduction in choreiform movement; however, this effect was lost when the results were reanalysed, excluding patients on antipsychotics, and larger and longer studies have not demonstrated beneficial or neuroprotective effects. One RCT investigating the use of amantadine (100mg tds for 2 weeks) demonstrated only subjective improvement in quality of life scores reported by patients, with no changes in objective measures of choreiform activity. Another RCT reported an 18% improvement in chorea by amantadine treatment, compared to 5% with placebo. Based on these findings, the AAN suggests these agents may be considered as second-line agents in the treatment of HD chorea.

Unfortunately, there are no effective treatments available for motor impersistence (the ability to maintain a sustained voluntary action, e.g. tongue protrusion), abnormal eye movements, and gait, speech, and coordination disturbance.

Sydenham's chorea (St Vitus' dance)

Sydenham's chorea is an infrequent manifestation of rheumatic fever in children. The condition is usually self-limiting. In over 50% of patients, complete remission occurs in 2–6 months. However, half of the remaining patients may have mild to moderate persistent symptoms after 2 years, and recurrence has been reported in up to 25% of patients. Where chorea is troublesome or there is psychiatric disturbance, patients may benefit from a trial of sodium valproate or carbamazepine.

Treatment and evidence base

There have been no RCTs investigating the treatment of Sydenham's chorea. The evidence for pharmacological therapy is based on case reports and small unblinded prospective studies without control arms. A study in 15 children found valproic acid (10–15mg/kg/day) resulted in improvement in 13 children within 1 week. Carbamazepine (4–10mg/kg/day) was also shown to have a beneficial effect in one small prospective study of nine children; the majority improved within 4 weeks. Carbamazepine and valproate have been compared in an un-blinded prospective study (n = 24). Both agents resulted in clinical improvement; however, no significant difference was noted in time to clinical improvement, time to complete remission, duration of therapy, or recurrence rates between the two drugs.

Myoclonus

Myoclonus is the sudden involuntary jerking of a muscle group, caused by the rapid contraction of agonist and antagonist muscles (positive myoclonus) or loss of tonic muscle tone (negative myoclonus, e.g. seen in hepatic encephalopathy).

The origin of myoclonus may be cortical, subcortical, spinal, or peripheral. Clinical features may help to differentiate one from the other.

- Cortical myoclonus: the commonest form; predominantly affects the face and distal limbs (arms > legs, reflecting sites of greatest cortical representation, as myoclonus is generated in the contralateral prefrontal cortex) and is often stimulus-sensitive.
- Subcortical myoclonus: this often affects multiple muscle groups and is frequently bilateral, affecting the axial or proximal muscles. Contractions are often of longer duration than those seen in cortical myoclonus and are frequently stimulus-sensitive (e.g. auditory).
- Spinal: these are jerks of groups of muscles innervated by the same nerve root. They can be stimulus-sensitive and may occur during sleep as well as when awake.
- Peripheral: caused by a lesion to a nerve, plexus, or root. The onset of myoclonus by denervated muscles may be delayed post-injury.

Treatment

Any underlying medical condition should be treated first (e.g. liver or renal disease resulting in a metabolic encephalopathy). Symptomatic treatment is achieved through increasing GABA-ergic neurotransmission. All treatments should be commenced at a low dose and gradually increased to achieve adequate control. Combination therapy is frequently required, with treatment often being only partly successful.

- Cortical myoclonus:
  - first line: levetiracetam or piracetam;
  - second line: sodium valproate, primidone, or clonazepam.
- Subcortical and spinal myoclonus:
  - first line: clonazepam.
- Peripheral myoclonus (e.g. hemifacial spasm):
  - first line: botulinum toxin.
- Drugs to avoid: carbamazepine, gabapentin, and phenytoin are known to exacerbate myoclonus and myoclonic epilepsy.

Evidence base

As cortical myoclonus is related to myoclonic epilepsy, antiepileptic agents are often the first drug of choice. There is little strong evidence for the treatment of myoclonus. Piracetam (2.4–16.8g/day) has been shown in a small placebo-controlled, double-blind, cross-over trial of cortical myoclonus (n = 21, duration 14 days) to improve motor impairment, writing, and functional disability. It is well tolerated; however, large doses (up to 24g/day) may be required for adequate control. Levetiracetam (2–3g/day), which is an analogue of piracetam, may be effective and is better tolerated with fewer side effects. Small observational studies and expert opinion highlight clonazepam

(up to 15mg/day) and sodium valproate (up to 1200–2000mg/day) are also effective for cortical myoclonus. Standard antiepileptic medications do not appear to be effective in subcortical myoclonus. Clonazepam has been trialled in small studies and is used first-line in subcortical myoclonus, based on expert opinion.

A Cochrane review investigating the use of botulinum toxin for hemifacial spasm established that there was only one small RCT that has investigated this application (n = 11). The trial found that objective improvements were reported in 84% of botulinum-treated patients.

Restless legs syndrome

Patients with restless legs syndrome (RLS) typically describe an intense restlessness and unpleasant creeping sensation deep inside the lower legs. Symptoms appear when the legs are at rest and are worst in the evening and at night. Patients are forced to move their legs, often getting out of bed to do so. This can affect sleep quality and often results in insomnia. An AD-like inheritance is noted in a majority of cases. RLS can be of primary (idiopathic) or secondary origin. Secondary RLS may be caused by:

- iron deficiency;
- chronic renal disease (especially those on dialysis);
- peripheral neuropathy (vitamin B12 and folic acid deficiency, especially in older individuals or pregnant women);
- PD;
- pregnancy.

Treatment

The need for treatment should be based on the frequency of troublesome symptoms and the effect that these have on sleep quality. For patients with infrequent bouts of RLS, treatment on an as-required basis may be appropriate. Avoidance of aggravating substances, such as nicotine, caffeine, and alcohol, should be advised. Stretching and light exercise may also help. The following recommendations are in line with advice provided by the American Academy of Sleep Medicine and the EFNS/European Neurological Society (ENS)/European Sleep Research Society (ESRS) joint guidelines:

- first line: DAs (e.g. pramipexole, ropinirole, and rotigotine);
- second line: levodopa, gabapentin enacarbil, or opioids;
- third line: cabergoline, pregabalin, or carbamazepine;
- Other: benzodiazepines (short term to improve sleep quality).

Additionally, iron supplementation in those known to be deficient can improve symptoms.

Seventy per cent of patients treated with levodopa, and to a lesser extent DAs, are associated with the phenomenon of 'augmentation'. Patients report the onset of symptoms earlier in the day, spread to the trunk and upper limbs, and reduced duration of treatment effect.

Evidence base

- *DAs*: DAs pramipexole, ropinirole, and transdermal rotigotine have been shown to be effective in RCTs for the short- and long-term treatment of RLS. Their longer half-lives and lower incidence of augmentation mean that they are preferred to levodopa as first-line treatment. Of the DAs, rotigotine appears to be associated with the lowest incidence of augmentation (13%). Cabergoline (0.5–3mg/day) is one of the most studied agents for RLS and is highly effective. Its use, however, is not advised due to the risk of ergot-related side effects (e.g. valvular fibrosis), particularly at doses over 3g/day. Patients already taking cabergoline require regular echocardiography and X-rays to monitor for the onset of valvular dysfunction and pulmonary fibrosis.
- *Antiepileptics*: gabapentin enacarbil (600–1200mg daily), gabapentin (800–1800 mg daily), and pregabalin (150–450mg daily) have all have

been shown to be very effective and well tolerated in treating RLS, with the strongest evidence for gabapentin enacarbil. This is a new prodrug of gabapentin with greater bioavailability and is indicated in those who cannot take dopaminergic agents and may be of particular use in patients with co-morbid neuropathic pain.

- *Levodopa*: due to the significant risk of augmentation with levodopa (in particular at doses >200mg/day), it is now mainly used in diagnosis of RLS and for patients requiring intermittent treatment. A Cochrane review of nine RCTs investigating the use of levodopa in moderate to severe RLS found that it improved symptoms, sleep, and clinician ratings, compared to placebo. Active comparison trials between levodopa and DAs suggest that DAs may be better at controlling RLS symptoms and improving quality of life; however, CIs in these trials were large, meaning that firm conclusions could not be made.
- *Opioids and benzodiazepines*: opioids may be effective where other treatments have failed; however, their potential for abuse and side effect profile should be considered before use. Short-term benzodiazepines may also be useful to improve quality of sleep in refractory cases.

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Chapter 11

Dementia

Introduction

Dementia is a progressive neurodegenerative condition which affects 5–7% of people aged over 65 throughout the world. The commonest subtype is Alzheimer's disease (AD), estimated in the UK to account for 62% of disease. This is followed by vascular dementia (VaD) (17%), then DLB (4%), frontotemporal dementia (FTD) (2%), PDD (2%), and rarer forms. It is quite common for patients to suffer from dual, or even three, pathologies, most commonly a combination of AD and VaD (mixed dementia accounts for ~10% of cases).

The DSM-5 defines dementia (specifically termed as a 'major neurocognitive disorder' in this edition) as an acquired significant cognitive impairment in a minimum of one of the following domains:

- learning and memory;
- social cognition;
- language;
- executive function;
- complex attention;
- perceptual motor function.

The deficit must lead to an impairment of activities of daily living and involve a continuous cognitive decline from a previous high level of functioning. Dementia should only be diagnosed in the absence of delirium and psychiatric illness.

The management of dementia is multidisciplinary, with pharmacological treatment playing a relatively small role. Care should be focused on ensuring appropriate coordination of health and social services. Drug treatments are used to allow patients to maintain their functional independence for as long as possible and then to aid management of troublesome behaviours in late disease.

Alzheimer's disease

AD is the commonest form of dementia, affecting as many as 30% of those aged over 90. AD occurs sporadically and insidiously, and typically affects patients' episodic memory first, with relentless, slow progression to involve other domains—patients may ultimately experience a combination of problems, including language difficulties, visuospatial difficulties, dyspraxia, loss of executive functioning, and neuropsychiatric features.

The severity of AD needs to be assessed, as this will guide pharmacological treatment options. The most widely used method of assessing severity is the mini mental state examination (MMSE), which assesses orientation, recall, attention, calculation, language manipulation, and constructional praxis. The severity of AD is then stratified (maximum 30):

- mild: 21–26;
- moderate: 10–20;
- severe: <10.

Treatment

- Mild or moderate AD:
  - first line: donepezil, galantamine, or rivastigmine;
  - second line: memantine (moderate AD).
- Severe AD:
  - memantine (donepezil and rivastigmine can be used in the USA).

In the UK, NICE recommends that these drugs should be started by specialists and only continued if cognitive, functional, global, or behavioural symptoms are improving on serial follow-up. NICE suggests that cost, side effects, drug adherence, co-morbidities, drug interactions, and dosing profiles should be considered when choosing the most appropriate of the three anticholinesterase inhibitors (AChEIs) (see Anticholinesterase inhibitors, pp. 261–7). Cost-effectiveness comparisons undertaken by NICE show little difference between the three AChEIs for mild to moderate AD. Memantine is less cost-effective in moderate AD than AChEIs and hence should be used second-line for this indication. The AChEIs are relatively safe drugs; however, they can exacerbate bradycardia and cardiac arrhythmias, which should be borne in mind before offering treatment. The risks are thought to be equivalent among all available drugs.

Treatment withdrawal

Clinically, improvement on AD medication, within the first 6 months of initiation, warrants long-term continuation for at least a year, with one retrospective study suggesting the treatment effect may last up to 5 years for some patients. However, most patients will return to pre-treatment levels of cognition 12–18 months after initiation. It is important to stress that AChEIs can have a pronounced effect on domains other than cognition that may justify continuation. There is, however, no consensus on how to estimate the clinical efficacy of treatment in severe AD (as the MMSE is a poor tool for discerning changes in cognitive ability at such severe levels of impairment) and when it may be appropriate to discontinue AChEIs or switch to memantine. In general, clinicians in the UK withdraw most AChEIs on a trial basis, to simplify drug regimes, as marketing authorization for

AChEIs stops, and when an MMSE score of 10 or less is reached. If there is a sudden or drastic decline, treatment is restarted. In the USA, licensing for donepezil and rivastigmine is extended into severe disease, primarily due to the recognized benefits on domains outside cognition.

Evidence base

AChEIs and memantine have been extensively investigated in AD. Multiple RCTs and meta-analyses have shown benefits of varying magnitude on cognition, behavioural symptoms (e.g. agitation, aggression), and functional outcomes (e.g. activities of daily living). Their safety and tolerability, in addition to clinicians' rating of patients, have also been assessed.

1. *Cognition*: in a 2014 meta-analysis of RCTs assessing the efficacy of AChEIs and memantine in patients with mild to moderate AD, statistically significant improvements in cognition, measured by differences in the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog) score, were seen with treatment, when compared to placebo, for all medications. The score ranged from −1.29 points mean difference with 20mg/day of memantine to −3.2 points mean difference with 32mg/day of galantamine. Clinical experience suggests most patients are started on donepezil in the first instance, but head-to-head comparisons of AChEIs have not shown significant differences in efficacy between drugs of this class. A meta-analysis of two RCTs comparing AChEIs and memantine demonstrated that, in mild to moderate disease, memantine has a smaller impact on cognition than AChEIs. Hence, it is used second-line to the AChEIs for this indication.
2. *Neuropsychiatric symptoms*: there is conflicting evidence on the effect AChEIs and memantine have on behavioural components of AD (i.e. depression, anxiety, sleep disturbance, and aggression). Donepezil and galantamine have both been found to improve behavioural outcomes in some, but not all, trials. Two meta-analyses published in 2014 agreed that there may be a small improvement of behavioural symptoms with galantamine, but only one concluded that this was the case for donepezil. Memantine and the other AChEIs were not found to have a beneficial effect on behaviour in both of these meta-analyses. As such, AChEIs and memantine are not licensed for treatment of these symptoms specifically. However, the benefits can be used to justify continuing treatment in those already taking it, as is the case in the USA.

Vascular dementia

VaD is the second commonest cause of dementia. Diagnosis is made on the basis of a combination of clinical features, the presence of vascular risk factors, and supportive neuro-imaging. The condition may be characterized by a stepwise progression of cognitive deficits, although onset can be subtle, probably due to accumulation of infarcts in non-eloquent areas of the brain or mixed pathology.

Treatment and evidence base

The treatment of VaD focuses on the prevention of recurrent strokes by modifying risk factors for cerebrovascular disease.

Risk factor management

1. *Hypertension*: very high or consistently low BP is associated with the development of VaD. There is some evidence suggesting that hypertension, particularly untreated hypertension in midlife, has a negative effect on cognition and can contribute to the development of dementia. In older adults, the importance of maintaining a high enough BP to provide adequate cerebral perfusion has been highlighted, with studies suggesting that, in patients with persistently low BP, the relative risk of dementia is increased.

   There are no published clinical trials assessing the effect of anti-hypertensive medication on reducing the risk of dementia or cognitive decline, as a primary endpoint, although several have looked at dementia as a secondary outcome measure. The *SYST-EUR* (Systolic Hypertension in Europe study), a randomized, placebo-controlled trial of nitrendipine, a calcium channel blocker, (n = 2418) found that active treatment reduced dementia risk by 50% (3.8 vs 7.7 per 1000 person years; p = 0.05), with a median follow-up of 2 years. The *PROGRESS* study (Perindopril Protection against Recurrent Stroke study) (n = 6105) showed a non-significant reduction in risk of dementia by 12% in the treatment group. In a subgroup analysis of patients with recurrent stroke, there was a significant reduction in the risk of dementia by 34%. Hence, it is reasonable to manage hypertension in patients who have had a stroke to prevent the occurrence of VaD.
2. *Diabetes*: diabetes is an important risk factor for cardiovascular disease and stroke. One systematic review of 14 longitudinal studies found a 2.5-fold increase in the risk of developing VaD in patients with diabetes. Although there have been no RCTs investigating the effect of controlling blood glucose on the risk of developing, or the rate of progression of, VaD, observational studies have shown that rigorous control of blood glucose has been inversely correlated with cognitive decline.
3. *Hypercholesterolaemia*: epidemiological links between hypercholesterolaemia and VaD have been identified in several observational studies. There may also be a link with elevated cholesterol and the risk of AD; however, this evidence is less clear. Although there is no clear evidence that statins and other lipid-lowering agents lower the risk of VaD in patients with high cholesterol, they do lower the risk of cardiovascular disease and stroke, and hence intuitively should reduce the risk of VaD.

Antiplatelet agents

Aspirin is widely used in the management of VaD; however, there are no RCTs to confirm that its use can reduce the risk of developing dementia or reduce the rate of cognitive decline in patients with existing VaD.

Cholinesterase inhibitors and memantine

The justification for the use of cholinergic agents in VaD is based on the profound reduction in cholinergic markers found in the hippocampus, frontal areas, and temporal cortex in patients with this condition. Several meta-analyses show small cognitive improvements with AChEIs and memantine in patients with VaD. However, the benefits are not clinically significant enough to warrant licensing for VaD. Given the possible association of VaD with AD and the difficulty that lies in excluding AD in patients with VaD, off-label use is often seen.

Dementia with Lewy bodies

DLB is a syndrome characterized by progressive cognitive decline, combined with a triad of fluctuating cognition, recurrent visual hallucinations, and motor features of parkinsonism. It is also often accompanied by REM sleep disorder and severe neuroleptic sensitivity. Dementia must precede or accompany the spontaneous onset of parkinsonism, to differentiate DLB from PDD. Management includes early detection, investigation, diagnosis, and treatment of cognitive impairment. Behavioural and neuropsychiatric symptoms, movement disorders, autonomic dysfunction, and sleep disorders should also be addressed. Cognitive dysfunction and neuropsychiatric symptoms can be improved by educating patients and caregivers on the nature of the disease and increasing social interaction and environmental stimuli.

Treatment

- First line: rivastigmine.

The pharmacological management of DLB is challenging because of the mixture of autonomic, neuropsychiatric, cognitive, and motor dysfunction not seen in AD. These features tend to be unpredictable, and treatment of one may exacerbate the other. This particularly applies to the treatment of neuropsychiatric symptoms and parkinsonism, which may exacerbate each other (for further information on the management of motor aspects of DLB, see Chapter 9, Parkinson's disease and parkinsonism).

Rivastigmine is licensed for use in PDD in the UK and USA for its behavioural, rather than cognitive, benefits. As many see DLB and PDD as a spectrum of disease, it is also frequently used in DLB. Although donepezil appears to be of greater benefit than rivastigmine, in terms of improvements in cognition and caregiver burden, it is not licensed for use in DLB but is often used off-licence in these patients. Galantamine has not been studied in DLB but can also be used off-licence for the same reason.

Evidence base

1. *Rivastigmine:* in one 20-week, double-blind, placebo-controlled trial of 120 patients with DLB given either 6–12mg/day of rivastigmine or placebo, 63% of the rivastigmine arm showed at least a 30% improvement in baseline neuropsychiatric testing, compared to placebo ($p = 0.001$). Symptom domains improving on rivastigmine included apathy, anxiety, indifference, delusions, hallucinations, aberrant motor activity, and attention. There was no effect on the MMSE or clinical global change-plus scale.
2. *Donepezil:* in a 12-week RCT of 140 patients (Donepezil-DLB Study), mean changes in MMSE scores were significantly higher in the donepezil-treated groups (5mg: 3.4, $p < 0.0001$; 10mg: 2.0, $p < 0.001$) than placebo (−0.4). Statistically significant improvements in behaviour were also noted, compared with placebo (5mg: −5.80, 95% CI −12.4 to 0.8, $p = 0.047$; 10mg: −8.3, 95% CI −15.8 to −0.9, $p = 0.019$). Caregiver burden was significantly reduced with 10mg/day of donepezil, compared with placebo (mean change in Zarit caregiver burden inventory of −9.2, 95% CI −15.3 to −3.0), but not with 5mg/day.

3. *Memantine:* there is no substantial evidence for efficacy of memantine in DLB. One industry-funded, double-blind, randomized, placebo-controlled trial in 41 patients showed improvements in behavioural symptoms (difference −5.9, 95% CI −11.6 to −0.2; $p = 0.041$) and improved clinical global impression of change scores (difference −0.6, 95% CI −1.2 to −0.1; $p = 0.023$) in patients taking 20mg/day, compared with placebo. No significant benefits were noted for cognition or reduction in caregiver burden. Moreover, there are anecdotal data suggesting a worsening of delusions and hallucinations in patients with DLB taking memantine.

Parkinson's disease dementia

Dementia is thought to occur in 31–41% of patients with PD. Increasing age, duration and motor severity of PD, and the presence of visual hallucinations, as well as specific genetic mutations, including the ATPase gene and apolipoprotein gene, have been positively correlated with PDD.

PDD is diagnosed when a patient who has had PD for 1 year or more develops dementia. Compared to AD, the cognitive decline is characterized predominantly by attention, visuo-perceptive, and visuo-constructive deficits.

Treatment

- First-line: rivastigmine.

Evidence base

Of the anti-dementia drugs, rivastigmine has the strongest body of evidence. The *EXPRESS* study (EXelon in PaRkinson's disEaSe dementia study) was a parallel-group, double-blind, placebo-controlled trial ($n = 541$) investigating the use of rivastigmine in patients with PD and mild to moderate dementia (MMSE 10–24). Those on the treatment arm showed an 8.8% improvement from baseline cognitive scale scores, while the placebo arm showed a 2.9% worsening ($p < 0.001$). Worsening of parkinsonian symptoms (particularly tremor) was reported more frequently in the treatment arm (27%, compared to 16%); however, this was not statistically significant.

Trials investigating the effects of donepezil, galantamine, and memantine have not shown convincing evidence of cognitive improvement with these drugs. Of the drugs used to treat PDD, the MDS evidence-based review found only rivastigmine to have proven efficacy in PDD.

Frontotemporal dementia

The FTDs are a group of clinical syndromes in which degeneration of the frontal and anterior temporal lobes is seen. Although the syndromes are clinically and pathologically heterogeneous, abnormal behaviour predominates in FTD.

Treatment

There is some evidence to suggest that multimodal rehabilitation for patients and education for caregivers are useful. There is very little evidence that pharmacological interventions help, although SSRIs and antipsychotics may be used for the management of behavioural problems, on the basis of evidence from small trials and case series. CNS stimulants, e.g. dexamfetamine and methylphenidate, have also been used for the management of behavioural problems. However, different trials have given conflicting results, hence their use is still considered experimental. There is no convincing evidence that AChEIs or memantine are useful in modifying behaviour or improving cognition in FTD.

Mixed dementia

Pathological studies have suggested that coexisting vascular pathology exists in around 25% of patients with AD. Additionally, pathological PD is present in around 25% of AD patients, and 50% of cases of DLB are associated with AD pathology.

Treatment

There have been a relatively small number of trials of AChEIs in mixed dementia. However, given that mixed dementia is an overlap of pathologies, treatment benefits may be extrapolated from trials in other forms of dementia. Mixed dementia should be managed according to the condition that is thought to be the predominant cause of the dementia.

Evidence base

There is very little evidence from controlled trials for the management of mixed dementia. Evidence for use of different agents are derived from purer forms of dementia. There are small placebo controlled studies of patients with Alzheimer's disease and vascular risk factors and Alzheimer's with cerebrovascular disease suggesting both rivastigmine and galantamine respectively, result in significant improvement in both cognitive scores and scales of activities of daily living. Hence it is reasonable to use cholinesterase inhibitors on at least a trial basis if there is suspicion that the patient's dementia syndrome is at least in part as a result of Alzheimer's pathology.

Mild cognitive impairment

The National Institute on Aging–Alzheimer's Association has suggested the following features as core clinical criteria for mild cognitive impairment (MCI):

1. a fall in cognition reported by a patient or informant, or observed by a clinician;
2. an objective impairment in one or more cognitive domains, usually including memory;
3. no change in functional independence;
4. no dementia.

MCI is believed to be a precursor to AD, particularly the amnestic subtype, with 5–10% of patients progressing to AD annually. It remains, however, a somewhat contentious diagnosis, and some studies have reported that around 40% of those diagnosed will revert to normal over 1–3 years. There are no licensed treatments for MCI. Trials have produced conflicting data. A 2012 Cochrane review of nine double-blind, placebo controlled trials assessing the use of AChEIs in patients with MCI (n = 5149) established that AChEIs did not significantly improve cognitive test scores or convincingly prevent progression to dementia.

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Chapter 12

Spasticity

Introduction

Spasticity can be defined as a velocity-dependent increase in muscle tone seen in a UMN syndrome. It is most commonly seen in MS, stroke, and cerebral palsy, but it may also occur in brain and spinal cord injury or indeed any pathology that involves descending motor pathways. In general, spasticity develops gradually over days, weeks, and months, following the development of a UMN lesion.

In a patient with spasticity, the neurological examination reveals increased tone of the affected limb(s). Resistance is increased on passive stretch in a velocity-dependent manner, as exemplified by the supinator catch. Spasticity is usually accompanied by other UMN signs, including pyramidal pattern weakness, brisk reflexes, clonus, spastic dystonia, and extensor plantar responses. Sometimes, a 'clasp-knife' phenomenon is seen where more sustained force leads to a sudden, paradoxical reduction in tone. Spasticity can generally be distinguished clinically from other causes of increased tone, including rigidity, gegenhalten, and catatonia. The severity of spasticity may vary considerably, from being a clinical sign with no functional impact to a gross increase in tone interfering with mobility, transfers, and personal care. Severe untreated spasticity may result in secondary biomechanical effects, including tendon shortening, contractures, and heterotopic ossification.

Treatment

Not all patients with spasticity require pharmacological treatment. Spasticity is not always detrimental and can have some benefits. Trunk muscle stiffness can help with sitting upright and with transfers, and spasticity of hip and knee extensors can aid standing, transferring, and walking. Commonly used agents, such as baclofen and tizanidine, can cause muscle weakness and sedation. Hence, patients with mild spasticity and stable symptoms may derive little benefit from oral anti-spasticity agents, and treatment could actually be detrimental. In general, patients with problematic spasticity are best managed by a multidisciplinary rehabilitation team using a goal-centred approach.

Non-pharmacological methods of treatment

- *Physical aids and mobility training*: occupational therapists and physiotherapists may make progress with splinting and positioning programmes (such as with a T roll or an upper limb splint), and regular standing in a standing frame has also been shown to be helpful. Stretching and exercise, however, do not appear to have a significant effect on spasticity per se, although exercise may improve strength and function. A specialist wheelchair and seating assessment may also help with tone management of the limbs and trunk.
- *Treatment of exacerbating factors*: it is important to consider factors which may be exacerbating spasticity. Nociceptive, visceral, or somatic stimuli, including pressure sores, chronic urinary retention, or constipation, may all have an impact upon spasticity.
- *Surgery*: operative interventions can be useful in specific circumstances. A selective dorsal rhizotomy may be an option for young people with cerebral palsy. Usually several lumbar laminectomies are performed, and the dorsal nerve roots are isolated and tested with EMG. If they are shown to be associated with problematic spasticity, they are ablated. Other surgical options include tendon lengthening procedures to improve range and movement.

Pharmacological methods of treatment

As spasticity worsens, there comes a point when medical treatment needs to be started. A goal-orientated approach is generally adopted. For instance, in a patient with a spastic paraparesis, the aim might be to relieve nocturnal spasms which disrupt sleep or to alleviate leg stiffness and clonus when standing and walking. Following a stroke, spasticity at the elbow, or elsewhere in the affected arm, which has not responded adequately to early physiotherapy and splinting, may greatly benefit from botulinum toxin injections.

When oral anti-spasticity agents are used, a ‘start low and go slow’ approach can avoid unwanted side effects of sedation and weakness often seen with inappropriate dose escalation.

Systemic agents

- First line: baclofen or tizanidine.
- Second line: dantrolene.
- Gabapentin or pregabalin.
- Additional adjuncts: cannabinoids, benzodiazepines, or carbamazepine.

The $GABA_B$ receptor agonist baclofen or the $\alpha 2$-adrenergic antagonist tizanidine are usually first-line options. The efficacy of both drugs is comparable, but their side effect profiles differ, and, if a patient is intolerant of one, it may be worth a trial of the other. Liver function tests (LFTs) need monitoring with tizanidine, but blood tests are not required with baclofen. Either drug should be started at a low dose and titrated slowly (generally over several weeks), and occasionally patients will end up taking both. Dantrolene is an alternative. It acts directly on muscle tissue, and it can have a useful role as a second-line agent when baclofen and tizanidine are not tolerated. It does carry a risk of hepatitis, and careful monitoring of LFTs is required.

Other drugs that can be used include:

1. benzodiazepines such as clonazepam. These may be particularly useful for intermittent spasms, especially when sleep is disrupted;
2. gabapentin and pregabalin can be used as an adjunct to first-line therapies but are particularly useful when myelopathic pain is a problem;
3. carbamazepine is useful for paroxysmal tonic spasms in MS (when intermittent motor and/or sensory symptoms occur due to ephaptic conduction within a demyelinated lesion);
4. a cannabinoid oromucosal spray is licensed for the treatment of spasticity in MS.

Evidence base

A 2003 Cochrane database meta-analysis of anti-spasticity agents in MS included 26 placebo-controlled studies and 13 comparative studies. Only 15 of these studies used the Ashworth scale (a reliable measure of spasticity used to gauge the effectiveness of an anti-spasticity agent), and only three of the eight placebo-controlled trials showed a statistically significant difference. Many studies were of low quality. The authors concluded that no recommendations could be made for prescribing. There are even fewer data for the use of oral anti-spasticity agents in other conditions (with only a very limited number of small controlled studies in stroke, cerebral palsy, and spinal cord injury). A meta-analysis of studies investigating tizanidine concluded that there was insufficient evidence to recommend tizanidine over baclofen, or vice versa.

Localized treatments

1. *Botulinum toxin*: botulinum toxin injections are commonly used to treat focal or multifocal spasticity. Botulinum toxin may be useful in a stroke patient with a spastic upper limb (where the elbow, wrist, and fingers are held in a flexed position) when there is inadequate response to splinting and oral agents. Alternatively, children with cerebral palsy and spastic diplegia may benefit from botulinum toxin injections to treat a plantiflexed and inverted foot. Injections are given to a specific muscle or to several muscles. The effect wears off over 3–4 months, as nerve terminals re-sprout, and serial splinting during therapy is generally required.

Evidence base

The UK Royal College of Physicians has published guidelines listing 13 studies (ten placebo-controlled trials) using botulinum toxin to treat upper limb spasticity in stroke, traumatic brain injury, or in a mixture of CNS disorders, with evidence for a reduction in tone and some evidence for an improvement in function. Eight studies (six controlled trials, with one parallel study) investigated lower limb spasticity. Again there was some evidence for a reduction in tone and for an improvement in function.

2. *Phenol and alcohol ablation*: these neurolytic agents are sometimes used to treat focal spasticity, usually when lower limb regional spasticity involves large muscles and when the dose limits for botulinum toxin injections would be exceeded. Nerves targeted with phenol might include the obturator nerve for adductor spasm and the sciatic nerve for hamstring spasms. Spasticity may recur after several months.

Evidence base

A randomized-controlled pilot study comparing phenol and alcohol neurolysis of the tibial nerve after stroke found that both were effective at reducing spasticity but that alcohol neurolysis seemed to have more sustained benefits.

3. *Baclofen pump and intrathecal phenol injections*: when a patient continues to be severely affected by lower limb spasticity, despite a trial of oral agents at adequate doses and a period of rehabilitation, an intrathecal baclofen pump or intrathecal phenol administration may be indicated. In general, such a patient may have severe hamstring spasticity which is preventing them from being seated and/or severe hip adductor spasm, leading to difficulty in maintaining perineal hygiene and skin integrity.

   A baclofen pump is implanted surgically within the subcutaneous tissue overlying the abdomen. A catheter tracks subcutaneously from the pump to the lumbar subarachnoid space, and baclofen is infused continuously into this compartment. This reduces the systemic side effects, while allowing concentrated doses to be infused into the lumbar intrathecal space. The pump is programmed by a computer-controlled handheld device, and refilled with a needle every few months. Complications include pump infection, and there is a danger of severe rebound spasticity, akin to the NMS, if the pump is allowed to run out.

   Intrathecal phenol injections involve administration of phenol into the lumbar subarachnoid space. Typically, 1–2 injections are required, and this should result in a long-term reduction in spasticity. As impaired bladder and bowel function may also result, it is reserved for patients without any functional lower limb movement and who have already lost bladder, bowel, and sexual function and when other options have failed.

Evidence base

Many case series of intrathecal baclofen treatment have shown improvements in Ashworth scores in patients previously unresponsive to oral therapy. A small RCT (children with cerebral palsy randomized to receive an intrathecal baclofen pump either at 1 month or 6 months) found in favour of intrathecal baclofen vs continuing oral therapy. A case series of patients with quadriplegia showed that lower limb spasticity was reduced in most

patients, following an intrathecal phenol injection, but that it eventually returned in 80% (12 out of 15) of patients, although only as severe as previously in three.

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Chapter 13

Neuro-oncology

Introduction

Primary central nervous system tumours

In the UK, primary CNS tumours account for 2% of adult, and 20% of childhood cancers. They are second only to stroke as a cause of neurological death and place an enormous burden of suffering on patients, their families, and carers.

Brain metastases

Brain metastases are ~3–4 times more prevalent than primary CNS tumours. The commonest sources are lung cancer (30–60% of all cases, and the commonest primary source in men), breast cancer (20–30% of all cases, and the commonest primary source in women), melanoma, renal, and colorectal cancer. Overall 20–40% of patients with newly diagnosed cancer develop brain metastases.

Classification

Primary central nervous system tumours

There are over 150 different types of primary CNS tumours, according to the most recent WHO classification of brain tumours (2007). These are primarily divided by histological appearance into six main groups:

1. tumours of neuro-epithelial tissue, e.g. glioma;
2. tumours of cranial and paraspinal nerves, e.g. schwannoma;
3. meningeal tumours, e.g. meningioma;
4. haematopoietic neoplasms, e.g. lymphoma;
5. germ cell tumours, e.g. germinoma;
6. tumours of the sellar region, e.g. pituitary adenoma.

Gliomas are the commonest primary CNS tumour, accounting for ~60% of cases. These are thought to arise from glial cells. The most frequently occurring subtypes are astrocytomas, ependymomas, and oligodendrogliomas. They vary from low-grade benign tumours, such as pilocytic astrocytoma, to high-grade malignant tumours such as glioblastoma multiforme.

Glioblastoma multiforme (GBM) is the commonest primary CNS tumour in adults. It is a rapidly growing, destructive tumour, characterized histologically by vascular proliferation and/or necrosis. Prognosis is very poor, with median survival of 3–6 months if untreated and 15 months if treated optimally with surgery and chemoradiation.

Meningioma is the second most frequently occurring CNS tumour, accounting for ~20% of cases, and is the commonest benign primary brain tumour in adults. It arises from the meninges and typically grows slowly. Only a very small proportion are malignant. Most cases are curable by surgery alone or controllable with radiotherapy.

Primary CNS lymphoma (PCNSL) accounts for 3% of primary brain tumours and is associated with acquired immune deficiency syndrome (AIDS) and post-transplant patients. PCNSL shrinks rapidly with corticosteroids, hence these should be avoided, where possible, before definitive surgical biopsy (although complete radiological resolution with corticosteroids is unusual). In the majority of cases, PCNSL is rapidly progressive, and untreated median survival is ~6 weeks from diagnosis. Fitness for potentially toxic chemotherapy regimes is determined on the basis of organ function and comorbidities rather than chrononological age. Performance status often improves following initial therapy and may allow subsequent intensification of treatment. Schedules based around high-dose methotrexate are used for first-line remission induction in good performance patients and either oral temozolomide, whole brain radiotherapy, or corticosteroids alone in poorer performance patients. Some patients will be offered high-dose therapy followed by autologous stem cell transplantation. The 5-year survival rates can be as high as 80% in this group, but, for the majority of patients, median survival is about 60% at 2 years.

Tumour grading

Tumour grade is assigned according to specific morphological criteria, e.g. cellularity, presence of nuclear atypia, necrosis, and endothelial proliferation (see Table 13.1). Grades I and II are low-grade, while grades III and IV are considered high-grade, malignant neoplasms.

Table 13.1 WHO grading system for CNS tumours

Grade	Features	Prognosis (median life expectancy)
I	Slow-growing, usually benign	Excellent
II	Relatively slow-growing. Regarded as premalignant, with potential to progress to higher-grade neoplasms	Variable. Depends on histological subtype and resectability 5–15 years
III	Faster-growing tumours which can progress to grade IV	2–3 years
IV	Rapidly growing malignant neoplasms, characterized histologically by necrosis and/or vascular proliferation	1–2 years

Treatment

Treatment modalities used in the management of CNS tumours comprise chemotherapy, radiotherapy, and surgery, depending upon a number of factors, including histology, tumour location and genotype, patient performance status, and patient preference (see Table 13.2).

Table 13.2 Treatment regimens for common CNS tumours

Tumour	First-line treatment	Treatment of recurrence*
Low-grade glioma (I, II)	Surgery is potentially curative if grade I and complete resection. Radiotherapy if inoperable followed by chemotherapy with PCV or temozolomide	PCV or temozolomide if adequate performance status
Anaplastic astrocytoma/ oligodendroglioma	Maximal safe resection with post-operative radiotherapy ± PCV or temozolomide ± carmustine implant	PCV or temozolomide if adequate performance status
Glioblastoma multiforme	Maximal safe resection and chemoradiation with low dose temozolomide followed by 6 cycles of adjuvant temozolomide	Further surgery ± carmustine implant ± PCV or temozolomide + experimental agents e.g. anti-VEGF inhibitors, immune checkpoint inhibitors
Meningioma (grade I)	Surgery is potentially curative if complete resection and low grade, or stereotactic radiosurgery	Further surgery or radiotherapy
Primary CNS lymphoma	Patients with good performance status: polychemotherapy with high-dose methotrexate or high-dose chemotherapy with autologous stem cell transplant Patients with poor performance status: less intensive methotrexate as part of a regimen, e.g. with temozolomide	There is no accepted standard of care for the treatment of relapsed PCNSL. Wherever possible, patients should be offered participation in a clinical trial. Outside of a clinical trial, treatment should take account of performance status, neurocognitive function, and duration of response to previous lines of therapy.
Brain metastases	Whole brain radiotherapy for multiple lesions. Stereotactic radiosurgery for 1–4 small metastases Chemotherapy usually only if chemosensitive primary	As per first-line treatment, depending on patient performance status

* Repeat resection of recurrent brain tumours is only considered in a minority and depends upon accessibility and eloquence of the tumour site and patient performance status.

1. *Surgery*: surgery is important for establishing a tissue diagnosis, resection (potentially curative in low-grade tumours, particularly grade 1 gliomas and meningiomas, or palliative in higher-grade tumours), and relief of anatomical complications of tumour mass, e.g. shunting for obstructive hydrocephalus and debulking surgery for raised ICP.

   Resection is rarely curative in the context of intra-axial adult low-grade gliomas, because of the degree of localized spread prior to resection, but radical surgery prolongs progression-free survival.
2. *Radiotherapy*: radiotherapy can be administered as external beam radiotherapy, directed at the tumour mass, or whole brain radiotherapy, the latter usually reserved for brain metastases or PCNSL. Primary brain tumours are treated with conformal fractionated radiotherapy, delivered over several weeks, or with highly focused treatment as either fractionated stereotactic radiotherapy or single-fraction stereotactic radiosurgery.

   Stereotactic radiosurgical techniques (SRT), such as the gamma-knife, are commonly used to treat small, localized extra-axial brain tumours, which are situated close to important structures, and cerebral metastases. As a general rule, SRT can only treat tumours up to a maximum diameter of 3.5–4.0cm and up to a volume of 20cc in multiple metastases. This technique is not useful in the management of intra-axial gliomas where tumour spread means that a localized approach is less effective.
3. *Chemotherapy*: brain tumour sensitivity to chemotherapy depends on tumour type. Most high-grade gliomas are relatively chemoresistant, with the exception of anaplastic oligodendrogliomas with co-deletions of chromosomes 1p and 19q. The blood–brain barrier limits access of systemically administered hydrophilic chemotherapeutic agents to the CNS. Novel routes of administration are therefore required, e.g. intralesional delivery of carmustine implants post-surgery.

   High-grade gliomas are most commonly treated with combinations of procarbazine, lomustine, and vincristine (PCV regimen), or the oral alkylating agent temozolomide. Bevacizumab, a monoclonal antibody which blocks the action of VEGF, impairs tumour angiogenesis and hence proliferation. It has demonstrated limited effectiveness in the management of recurrent glioblastoma. It does not prolong survival in newly diagnosed GBM.

   Chemotherapy with PCV has been shown to prolong survival when used adjuvantly with radiotherapy in adult low-grade gliomas. Chemotherapy is associated with significant side effects, most commonly myelosuppression. Patient performance status, tumour grade and type, side effect profile of the different agents, and patient preference should inform treatment decisions.

Management of complications

Raised intracranial pressure

Clinical features of raised ICP include symptoms of headache, vomiting, and visual disturbance (obscurations, scotomata or enlarged blind spots, diplopia), progressing to the Cushing's triad of bradycardia, hypertension, and respiratory depression, and ultimately depressed consciousness and coma. There may be focal neurological deficits from the underlying pathology, and false localizing signs, such as cranial nerve VI palsies, and herniation syndromes.

Aetiology

Raised ICP is the final common pathway for many intra- and extracerebral pathologies, the commonest mechanisms being CSF accumulation, mass effect, venous congestion, or vasogenic oedema, either alone or in combination.

Raised ICP in brain tumour patients is usually treated by corticosteroids and surgical debulking, the urgency of which is dictated by the patient's level of consciousness and neurological deficits. The vast majority of patients with brain tumours have normal levels of consciousness and therefore can be treated with oral dexamethasone, with the intravenous route being reserved for the rare patient with depressed consciousness and peri-operatively. Dexamethasone is the preferred corticosteroid due to its markedly lower mineralocorticoid effect, lower risk of psychosis, and long half life. Maintenance therapy is usually given orally at 2–16mg/day 2–4 divided doses, depending on the degree of oedema and initial response.

Emergency management of acute rises in intracranial pressure in the context of CNS malignancy is similar to that in severe vascular and infective processes. It is best carried out in conjunction with intensive care and neurosurgical teams, and detailed management is beyond the scope of this book. The broad principles include:

1. Alleviating factors that can further raise ICP including seizures, hypercapnoea, hypoxia and high blood pressure secondary to pain, and agitation. These include paracetamol, cooling, head elevation to 30 degrees, sedation, and controlled ventilation.
2. ICP reduction with hyperosmolar therapy, either intravenous hypertonic saline or mannitol, can have a short temporising effect.
3. Dexamethasone is often used to control vasogenic oedema. Doses of 8–16mg intravenously can be used in the acute situation.
4. Definitive surgical management including surgical evacuation/debulking of brain lesions, CSF drainage/shunting, or decompressive craniectomy may be indicated depending on the underlying cause of raised ICP.

Seizures

Seizures are common complications of CNS tumours and tumour surgery. An estimated 80% of patients with gliomas experience seizures during the course of their illness. Seizures are frequently the presenting symptom of low-grade gliomas and are typically focal, with or without

secondary generalization. Levetiracetam is now widely used as first-line treatment for brain tumour epilepsy, although a recent systematic review recommended more high quality prospective data assessing levetiracetam and other antiepileptic drugs in this population. Alternative treatments are the same as for focal onset seizures (See Chapter 3, Epilepsy). Another meta-analysis suggests that levetiracetam is superior to phenytoin and sodium valproate as a prophylactic anti-epileptic drug in brain tumor surgery. However, best evidence and the AAN practice parameters advise against prophylactic treatment in patients with tumours but who have not as yet had a seizure.

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Chapter 14

Sleep disorders

Introduction

Sleep disorders are very common and usually underdiagnosed. They have an enormous impact on public health and productivity, with substantial financial implications for society. Mechanisms regulating normal sleep and sleep disorders are incompletely understood. This has implications for management of sleep disorders, as causative mechanisms can rarely be targeted for treatment. There is a paucity of RCTs for several of the drugs that are commonly used to treat sleep disorders. Hence, many compounds are used off-licence, based on case studies and clinical experience, rather than evidence-based medicine.

Classification

The International Classification of Sleep Disorders, second edition (ICSD-2) divides sleep disorders into eight major categories:

1. insomnia (including primary and secondary subtypes);
2. sleep-related breathing disorders (including sleep apnoea syndromes);
3. hypersomnia of central origin (including narcolepsy);
4. circadian rhythm sleep disorders;
5. parasomnias (including disorders of arousal in non-REM sleep and RBD);
6. sleep-related movement disorders (including periodic limb movements of sleep (PLMS));
7. isolated symptoms;
8. other sleep disorders.

Management of sleep disorders

The commonest sleep disorders are discussed in further detail below. With all of these conditions it is often equally important to identify and treat co-morbid conditions such as obstructive sleep apnoea (OSA), nocturia, pain, and mood disorders, which may further impair the quality of sleep. OSA is not discussed further below but should be considered in all patients with poor quality sleep, a typical body habitus and symptoms of excessive daytime sleepiness, CO_2 retention, and/or nocturnal apnoeic episodes.

Insomnia

Insomnia is the commonest sleep complaint, affecting up to 10–15% of the general population. It is defined as difficulty in getting to sleep, staying asleep, early wakening, or non-restorative sleep, despite adequate opportunity for sleep, which results in daytime functional impairment or distress.

Treatment

A wide range of drugs are used in the treatment of insomnia, with a variable level of evidence to support their efficacy.

In the short term, there are several controlled trials that support the use of both benzodiazepines and the so-called 'Z-drugs' (zopiclone, zolpidem, and zaleplon). Both of these drug classes work by enhancing the inhibitory effect of γ-aminobutyric acid (GABA). Although the Z-drugs were initially marketed as more effective and less addictive than the benzodiazepines, meta-analyses and reviews conducted so far have suggested that there is little added benefit to be derived from the use of Z-drugs, compared to short-acting benzodiazepines, such as temazepam, although well-controlled comparative studies are rare. All benzodiazepines and Z-drugs have the potential for addiction, and hence use of all of these drugs should be restricted to as short a duration as possible, certainly <2 weeks.

In the longer term, there are several treatment options.

1. *Psychological treatment*: CBT has been shown to be very effective, but unfortunately availability is often limited.
2. *TCAs*: although commonly used, there are currently no studies that show TCAs improve sleep in the long term, but there are some indications that other sedating antidepressants, such as trazodone, may improve insomnia and increase slow-wave sleep.
3. *Melatonin*: more recently, melatonin has been licensed for use in insomnia in people over 55 years of age. This is usually well tolerated and can provide substantial improvement in sleep for 50% of patients (vs 15% with placebo; $p = 0.018$). It is not clear if the indication will, in the future, also include younger patients.
4. *AEDs*: although not licensed for sleep-related problems, the AEDs gabapentin and pregabalin are increasingly used to treat insomnia, with good results, in particular if there is concomitant anxiety or RLS.

Narcolepsy

Narcolepsy is a chronic neurological disorder, in which the brain is unable to regulate sleep–wake cycles. Specifically, features of REM sleep intrude into wakefulness and non-REM sleep. The four cardinal symptoms are:

1. excessive daytime sleepiness;
2. cataplexy;

3. hypnogogic or hypnopompic hallucinations;
4. sleep paralysis.

Only 10–15% of patients with narcolepsy have all four features. Often there is also disrupted nocturnal sleep, with frequent arousals and parasomnias, which contribute to excessive daytime sleepiness.

Treatment

Treatment for narcolepsy is symptomatic.

1. Excessive daytime sleepiness:
   - first line: modafinil;
   - second line: dexamfetamine or methylphenidate.

Stimulants are used to manage excessive daytime sleepiness. Modafinil is used as first-line treatment, in view of robust efficacy data, a favourable side effect profile, and a low risk that tolerance may develop. Amphetamine derivatives dexamfetamine and methylphenidate are useful second-line agents but are associated with potentially severe vascular and psychiatric side effects.

2. Cataplexy and other REM-related symptoms (sleep paralysis and hallucinations) are usually treated with antidepressant medication. Clomipramine, fluoxetine, and venlafaxine have been shown to be of benefit in small series of patients only, and the evidence base for this treatment is limited, despite being common clinical practice. More recently, sodium oxybate (γ butyric acid) has been shown in RCTs to reduce both cataplexy and excessive daytime sleepiness. Sodium oxybate works by improving nocturnal sleep and is taken at night only. Despite good evidence for its efficacy, its wider use is limited by its cost.

Circadian rhythm sleep disorders

Circadian rhythm sleep disorders are characterized by disruption of the normal timings of sleep and wakefulness. Delayed sleep phase syndrome, where sleep onset occurs substantially later than conventional sleep, is the commonest and can be mistaken for insomnia. In the rare advanced sleep phase syndrome, the opposite occurs, and sleep is substantially earlier than normal.

Treatment aims to realign the circadian system with the conventional 24h cycle, using a combination of melatonin and light-box therapy (phototherapy).

Parasomnias

Parasomnias are abnormal events occurring in association with sleep and are classified according to the sleep stage in which they occur. The commonest are non-REM parasomnias, which are incomplete arousals from deep non-REM sleep and include night terrors, sleepwalking, and confusional arousal. They can sometimes involve violent or complex behaviour.

Treatment

For the majority of patients, medical treatment is not required. The reassurance of a formal diagnosis and avoidance of potential triggers, such as sleep deprivation, are sufficient. A minority with frequent episodes, resulting in sleep disruption and excessive daytime sleepiness, or who present with injurious or dangerous behaviour require medical treatment. Clonazepam, a long-acting benzodiazepine, or less commonly antidepressants, such as paroxetine, are used. Both approaches probably work by reducing the number

of arousals. It should be noted that all of the drugs used to treat non-REM parasomnias may paradoxically worsen symptoms, so careful monitoring is essential.

REM sleep behavioural disorder

During REM sleep, muscles are normally atonic. RBD is characterized by loss of this atonia, resulting in the patient acting out their dreams. RBD is associated with neurodegenerative conditions, most commonly PD, and can predate the onset of extrapyramidal symptoms by many years. In younger patients, RBD may be seen in association with narcolepsy or treatment with antidepressant medications, or alternatively it may occur in isolation.

Treatment

When treatment is indicated, clonazepam is often effective but can produce daytime sedation and exacerbate sleep-related breathing disorders, e.g. obstructive sleep apnoea. Zopiclone was found to be effective in a small study. Recently melatonin, often at higher doses of 5–10mg nocte, has been shown to be effective in treating RBD as well.

Periodic limb movements of sleep

PLMS are repetitive, stereotyped limb movements that occur every 5–90s during sleep. If this results in arousal and sleep maintenance insomnia, with consequent excessive daytime sleepiness, it is known as periodic limb movement disorder (PLMD). There is a strong association with RLS (see pp. 166–7), which may contribute to sleep-onset insomnia.

Treatment

Iron deficiency can exacerbate both RLS and PLMS, and iron supplementation should be given if ferritin levels are below 50 micrograms/L. Potential triggers, such as alcohol, nicotine, and caffeine, should be avoided. Clinical trials have mainly been performed for RLS, but it appears that PLMD responds to the same drugs, although this is usually an unlicensed prescription. Levodopa is effective but is frequently associated with augmentation, i.e. when RLS symptoms occur earlier in the day and potentially spread to other previously unaffected parts of the body. DAs (pramipexole, ropinirole, and rotigotine) can be effective and are less likely to result in augmentation. Alternatives include anticonvulsants, mainly gabapentin and pregabalin, and opioids such as codeine or tramadol.

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Chapter 15

Neurological infections

Introduction

This chapter considers the common neurological infections and the drugs available to treat them. Due to constraints of space and the knowledge that, for the less commonly used antimicrobials, guidance will be provided by infectious disease specialists, the majority of antimicrobials do not have individual drug monographs.

Pathophysiology

A wide variety of microorganisms target different components of the nervous system. In the CNS, this may result in isolated infection of the brain parenchyma (encephalitis), the meninges (meningitis), or the spinal cord (myelitis). Some of the organisms which cause encephalitis also cause an associated meningeal reaction or spinal cord inflammation, and these terms may be used alone or in various combinations to reflect what part of the neuroaxis is involved, e.g. meningoencephalitis, encephalomyelitis. Furthermore, infection may spread into the CNS from adjacent sites (parameningeal infections such as brain abscess, subdural empyema) or from the blood (endocarditis, septicaemia). Infection of components of the PNS is relatively uncommon. Special consideration needs to be given to neurological infections in the immunocompromised, as opportunistic infection by a different range of microorganisms commonly occurs.

Meningitis

Meningitis is the commonest CNS infection. In the UK, the majority of cases are self-limiting viral infections. However, differentiation between bacterial and viral meningitis on history alone is unreliable. CSF examination is helpful to distinguish between viral and bacterial meningitis, and may suggest other causes (see Table 15.1).

Community-acquired bacterial meningitis

The 'big three' microorganisms responsible for acute bacterial meningitis are *Streptococcus pneumoniae, Neisseria meningitides*, and *Haemophilus influenzae*. *Listeria monocytogenes* should be considered in the elderly or immunosuppressed. Empirical therapy with both antibacterials and antivirals is often advised (see Tables 15.2 and 15.3). In most settings, a third-generation cephalosporin and aciclovir are used, but meropenem or chloramphenicol are advised if there are concerns about penicillin allergy. Amoxicillin can be added if *L. monocytogenes* is suspected, and vancomycin added if penicillin-resistant pneumococci are suspected. The duration of antimicrobial therapy is usually 10–14 days.

Adjunctive steroids

Use of steroids in bacterial meningitis remains controversial. Adjunctive dexamethasone is thought to confer benefit, particularly in treatment of *H. influenzae* and *S. pneumoniae* meningitis. A large randomized trial of dexamethasone (10mg IV 15–20min before or with the first dose of antibiotic, then 6-hourly for 4 days) in adults with acute bacterial meningitis reduced the chance of an unfavourable outcome from 25% to 15% and mortality from 15% to 7%. The benefits were most striking in patients with pneumococcal meningitis.

Table 15.1 Typical CSF findings in CNS infections

	Viral meningo-encephalitis	Community-acquired bacterial meningitis	Tuberculous meningitis	Fungal	Normal
Opening pressure	Normal/high	High	High	High to very high	10–20cmH_2O
Colour	Clear	Cloudy	Cloudy/yellow	Clear/cloudy	Clear
Cells (cells/μL)	5–1000	100–50 000	25–500	0–1000	<5
Differential	Lymphocyte	Neutrophil	Lymphocyte	Lymphocyte	Lymphocyte
CSF:plasma glucose	Normal	Low	Low to very low (<30%)	Normal to low	66%
Protein (g/L)	0.5–1	>1	1.0–5.0	0.2–5.0	<0.45

Table 15.2 Empirical therapy in suspected community-acquired bacterial meningitis

Patient group	Common organisms	Initial IV antibiotics
Age 2–50 years	*N. meningitides* and *S. pneumoniae*	Third-generation cephalosporin ± vancomycin
Age >50 years	*N. meningitides*, *S. pneumoniae*, and *L. monocytogenes*	Third-generation cephalosporin ± amoxicillin ± vancomycin
Immunocompromised	*N. meningitides*, *S. pneumoniae*, *L. monocytogenes*, and Gram-negative bacilli	Third-generation cephalosporin, and amoxicillin ± vancomycin

Table 15.3 General recommendations for IV empirical antibiotic treatment doses

Treatment		Dose
Third-generation cephalosporin	Cefepime	2g every 8h
	Cefotaxime	2g every 4–6 hours
	Ceftazidime	2g every 8h
	Ceftriaxone	2g every 12h
Amoxicillin or ampicillin		2g every 4h
Chloramphenicol		1–1.5g every 6h
Meropenem		2g every 8h
Vancomycin		15mg/kg every 12h

Complications of acute bacterial meningitis

Patients with acute bacterial meningitis are at risk of various neurological and systemic complications and thus need intensive monitoring. Systemic complications of hypotension, septic shock, and adult respiratory distress are predictors of poor outcome. Hyponatraemia (serum sodium <135mmol/L) is found in 30% of patients. Hypernatraemia (serum sodium >143) occurs in 7% of patients, more commonly in those with severe disease, and is an independent predictor of poor outcome and mortality. Cerebral oedema, hydrocephalus (either communicating or obstructive), cerebral infarction from septic venous thrombosis or endarteritis, and seizures are the major neurological complications seen.

Chemoprophylaxis of acute bacterial meningitis

Chemoprophylaxis is indicated for close contacts of meningococcal meningitis cases and for patients with meningococcal meningitis treated with penicillin or amoxicillin monotherapy, as carriage is not reliably eradicated by these agents. Rifampicin 600mg bd PO for 2 days, ceftriaxone 250mg stat IM dose, ciprofloxacin 500mg stat PO dose, or azithromycin 500mg stat PO dose are believed to be equally effective.

Chronic meningitis

Chronic meningitis is defined as meningeal inflammation, diagnosed clinically and with supporting CSF findings, persisting for at least 4 weeks. Infections account for a proportion of cases (see Table 15.4), but neoplastic and other aseptic disorders should also be considered, and no cause is identified in up to a third of cases.

Table 15.4 Infective causes of chronic meningitis

Bacteria	Partially treated bacterial meningitis
	Tuberculosis (TB)
	Syphilis
	Lyme disease
	Other: *Brucella, Leptospira, Listeria, Mycoplasma*
Viral	HIV
	Herpesviruses: HSV, EBV
	Subacute sclerosing panencephalitis (measles)
Fungal	Blastomycosis, *Candida*, coccidiomycosis, cryptococcus, and histoplasmosis
Protozoa and metazoa	Acanthamoeba, *Angiostrongylus*, parasitic worms, and toxoplasmosis
Others that mimic chronic meningitis	Endocarditis/other embolic foci
	Parameningeal infection, e.g. epidural abscess/sinusitis

Tuberculosis

TB typically affects the CNS in three ways: TB meningitis, intracerebral tuberculomas, and spinal TB. Treatment requires combination therapy: rifampicin, isoniazid, pyrazinamide, and either ethambutol or streptomycin. Pyridoxine must be co-prescribed to prevent peripheral neuropathy due to isoniazid. A recent trial suggests 2 weeks of high-dose IV rifampicin may improve outcomes in CNS disease. An ongoing trial is investigating a role for fluoroquinolones. Treatment is for a minimum of 12 months, administered in conjunction with corticosteroids for the first 6–8 weeks in HIV-negative patients.

Encephalitis and myelitis

Encephalitis and myelitis may arise from post-infectious or post-vaccination autoimmune processes, as well as from direct infection of the parenchyma.

Acute encephalitis

Encephalitis means inflammation of the brain parenchyma and typically presents with a febrile illness, severe headache, nausea and vomiting, and reduced consciousness, often with seizures and focal neurological signs. Encephalitis can be caused by a range of viruses, the herpesviruses and arthropod-borne (arbo-) viruses being the most important (see Table 15.5). Other microorganisms can also cause encephalitis, particularly protozoa, such as *Toxoplasma gondii*, and bacteria, including *L. monocytogenes* and *M. tuberculosis* (see Table 15.6).

As a significant proportion of infectious encephalitis in the UK and USA is caused by herpesviruses, aciclovir is the treatment of choice. It is usually commenced if the initial CSF and/or radiological investigations are suggestive of viral encephalitis. However, if a delay of ≥6h is likely before an LP can be done or if the patient is deteriorating, it should be started empirically. In confirmed diagnoses, treatment is for 14–21 days or longer if the CSF viral polymerase chain reaction (PCR) remains positive. Steroids may be beneficial in the management of varicella-zoster virus (VZV) encephalitis, but their use in HSV encephalitis is currently subject to investigation in a large multicentre trial.

Table 15.5 Causes of acute viral encephalitis

SPORADIC	
Herpesviruses	HSV 1 and 2, VZV, EBV, cytomegalovirus (CMV), human herpesvirus (HHV) 6 and 7
Enteroviruses	Coxsackie viruses, echoviruses, enteroviruses, parechovirus, and poliovirus
Paramyxoviruses	Measles and mumps
Others (rare)	Adenovirus, influenza viruses, lymphocytic choriomeningitis virus, parvovirus, and rubella
GEOGRAPHICALLY RESTRICTED (mostly arboviruses)	
Africa	Rabies and West Nile
Asia	Dengue, Japanese encephalitis, Murray Valley encephalitis, rabies, and West Nile
Australasia	Japanese encephalitis and Murray Valley encephalitis
Europe/Middle East	Rabies, tick-borne encephalitis, and Tosana
The Americas	Dengue, Eastern and Western equine encephalitis, rabies, St Louis, and West Nile

Table 15.6 Other infectious causes of encephalitis

Bacteria	Actinomycosis, bacterial meningitis, *Brucella*, cat scratch fever, erlichiosis, *Leptospira, Listeria*, Lyme disease, *Mycoplasma, Nocardia*, relapsing fever, Rocky Mountain spotted fever, Q fever, syphilis, TB, typhoid fever, typhus, and Whipple's disease
Fungi	Candidiasis, coccidioidomycosis, *Cryptococcus*, histoplasmosis, and North American blastomycosis
Parasites	Amoebiasis, cerebral malaria, cysticercosis, *Echinococcus*, toxoplasmosis, trichinosis, and trypanosomiasis

Myelitis

Commonly, myelitis is a primary or post-infectious autoimmune phenomenon, but occasionally direct infection can be the cause, in which case organisms to consider include viruses (VZV, HSV, CMV, EBV, West Nile, influenza, echovirus, HIV, hepatitis A, rubella, measles), *Mycoplasma*, Lyme disease, syphilis, and parasites.

Lyme disease

Manifestations of neuroborreliosis (*Borrelia burgdorferi*) include encephalitis, myelitis, and cerebral vasculitis and should be treated with IV ceftriaxone. Lyme disease may also cause optic neuropathies, painful radiculoneuritis, often affecting the upper trunk and back which may resemble AIDP or a plexopathy (Bannwarth's syndrome), or cranial nerve palsies, treated with PO doxycycline. There may be a late mild chronic polyradiculoneuropathy, with or without acrodermatitis chronica atrophicans (a characteristic progressive fibrosing skin rash caused by ongoing active infection). Guidance varies but typically early neuroborreliosis (symptoms present for ≤6 months) is treated for 14 days, and late neuroborreliosis for 21 days.

Brain abscesses and parameningeal infections

Brain abscesses

Brain abscesses arise by two main routes: local spread (from sinusitis, otitis media, mastoiditis, dental sepsis, penetrating head injury, or neurosurgery) or haematogenous spread (from valvular heart disease with right-to-left shunt, pulmonary arteriovenous fistula in hereditary haemorrhagic telangiectasia, suppurative pulmonary infection, or endocarditis). The commonest causative microorganisms are streptococci, staphlyococci, and anaerobes. In immunosuppressed individuals, opportunistic infection should also be considered.

Treatment

Empirical treatment is guided by the likely source of infection. Given the frequency of anaerobic organisms, metronidazole plays a key role. Treatment is usually for a minimum of 4–6 weeks and depends upon whether the abscess has been excised, aspirated, or managed solely with antibiotics. Duration can be guided by serum CRP measurements, with switch from parenteral to oral therapy once clinical improvement occurs and the CRP has begun to fall.

Subdural empyema

Subdural empyemas usually arise by local spread from frontal sinusitis, otitis media ± mastoiditis. Spread tends to be faster, and mortality is consequently high, ranging from 6% to 20%. The commonest organisms vary with initial site of infection, but are typically staphylococci or streptococci.

Epidural abscess

Spinal epidural abscesses usually arise from vertebral osteomyelitis or discitis, but other causes include spinal surgery or spinal anaesthesia, drug use, or local trauma. Intracranial epidural abscesses can also occur. In 60% of cases, the responsible organism is *S. aureus*, but Gram-negative anaerobic rods, streptococci, and *M. tuberculosis* are occasionally implicated.

Septic intracranial sinus thrombosis

Septic cavernous sinus thrombosis, and lateral or sagittal sinus thrombosis arise from facial infections in 50% of cases, sphenoid sinusitis in 30%, dental infection in 10%, and occasionally from otitis media, mastoiditis, or other local infections. Diabetes mellitus is a significant risk factor.

Neurological infections in the immunocompromised

Patients with compromised immune systems are prone to a range of opportunistic infections not commonly seen in immunocompetent patients. A wide variety of microorganisms can cause opportunistic infections, most commonly viruses and fungi, but occasionally bacteria and protozoa. Those of most relevance to clinicians in developed countries are summarized in Table 15.7.

Table 15.7 Opportunistic neurological infections in the immunosuppressed

Organism	Clinical syndrome	Treatment
Viruses		
CMV	Encephalomyelitis, brainstem encephalitis, radiculitis, retinitis	Highly active antiretroviral therapy (HAART) for HIV, ganciclovir, foscarnet, cidofovir
JC virus	PML in HIV, transplant recipients, natalizumab treatment for MS, other biological agents	No known treatment Responds to immune reconstitution in MS (PLEX to remove natalizumab), and HAART for HIV but not usually in immunosuppressed transplant recipients
HIV	HIV encephalopathy	HAART
VZV	Reactivation—shingles, post-herpetic neuralgia, myelitis, meningoencephalitis, vasculopathy with stroke, cranial neuropathies, cerebellitis	Aciclovir, famciclovir
Fungi	See Table 15.8	
Protozoa		
Toxoplasma	Commonly presents with headache, fever, and neurological deficit associated with multifocal lesions, less commonly as unifocal lesions or as an encephalitic syndrome	Sulfadiazine plus pyrimethamine, or clindamycin plus pyrimethamine
Acanthamoeba spp (*Naegleria fowleri, Balamuthia mandrillaris*)	Granulomatous amoebic meningoencephalitis (freshwater swimming)	Amphotericin B, rifampicin, fluconazole

(*Continued*)

Table 15.7 (*Contd.*)

Organism	Clinical syndrome	Treatment
Bacteria		
M. tuberculosis	Meningitis, brain abscess, spinal epidural abscess	Quadruple anti-TB therapy plus corticosteroids
L. monocytogenes	Meningitis, brainstem encephalitis	High-dose amoxicillin
Nocardia	CNS infection, brain abscess	Meropenem
Treponema pallidum	Neurosyphilis—meninges, brain, brainstem, spinal cord, nerve roots, and cerebral and spinal blood vessels	IV benzylpenicillin, or IM procaine benzyl penicillin plus probenecid od

Fungal infections

Risk factors include immunocompromise of any cause and living in endemic areas. Fungal pathogens encountered in the CNS include yeasts (*Candida, Cryptococcus*), moniliaceous moulds (*Aspergillus* spp., *Fusarium* spp.), dimorphic fungi (*Blastomyces, Coccidioides, Histoplasma*), and zygomycetes (*Mucor* spp., *Rhizopus* spp.). CNS infection occurs through haematogenous spread, CSF seeding, or direct extension. Untreated, these are rapidly fatal infections, and mortality is high, even with early aggressive treatment.

See Table 15.8 for typical clinical presentations and treatments of the commoner fungal CNS infections.

Table 15.8 Fungal infections of the CNS

Organism	Clinical	Treatment
Coccidioides	Meningitis with basal cistern enhancement	Fluconazole
Candida	Meningitis in the immunosuppressed, organ transplant recipients, or patients following neurosurgery, especially if with prosthesis. Numerous microabscesses on MRI	Amphotericin B plus flucytosine Fluconazole, posaconazole
Aspergillosis	Rhinocerebral infections, especially in diabetics, immunosuppressed Angioinvasive—multifocal haemorrhagic infarcts, cavernous sinus thrombosis	Surgical debridement High-dose amphotericin B Posaconazole, voriconazole
Cryptococcus neoformans	Cryptococcal meningitis in immunosuppressed, often with raised ICP. Rarely focal signs from cryptococcoma Gelatinous pseudocysts in basal ganglia on MRI	In HIV—flucytosine plus amphotericin induction, then fluconazole maintenance
Mucormycosis	Invasive and highly aggressive, with high mortality. Often rhino-orbital sinus infection, frontal lobe lesions, cavernous sinus lesions Risk factors: diabetes (diabetic ketoacidosis), neutropenia, malnutrition, iron overload in dialysis, IV drug users	Amphotericin B, posaconazole

Parasitic infections

Parasitic CNS infections are relatively common worldwide but rarely encountered in clinical practice in the UK, Europe, and the USA. The typical clinical presentations and treatment of the commoner CNS parasites are briefly outlined in Table 15.9.

Table 15.9 Parasitic infections of the CNS

Organism	Clinical syndrome	Treatment
Schistosomiasis	Cerebral disease (*Schistosoma japonicum*), myelopathy (*Schistosoma mansoni* and *Schistosoma haematobium*) Early infection asymptomatic or acute encephalitis/myelitis (Katayama fever)	Praziquantel Corticosteroids for Katayama fever
Trypanosomiasis	American trypanosomiasis (Chagas' disease, *Trypanosoma cruzi*)—acute meningoencephalitis West and East African trypanosomiasis (sleeping sickness, *Trypanosoma brucei*)—encephalopathy with headache and prominent somnolence	Nifurtimox, benznidazole Suramin, melarsoprol, pentamidine, eflornithine
Plasmodium spp.	Cerebral malaria—rigors, fever, encephalopathy with raised ICP, delirium, seizures, focal neurological signs, and coma	*Plasmodium falciparum*—IM or IV artesunate plus doxycycline (IV quinine is an alternative to artesunate if the latter is not available)
Toxoplasma	Single or multiple brain lesions	Sulfadiazine, pyrimethamine, and folic acid Co-trimoxazole Clindamycin
Cysticercosis	Multiple parenchymal, intraventricular, or subarachnoid (racemose) cysts—epilepsy, headache, hydrocephalus, stroke, neuropsychiatric symptoms Vasculitis, arachnoiditis, encephalitis	Albendazole ± corticosteroids. Anticonvulsants

Bacterial neurotoxins

In the developed world, botulism and tetanus are rare, but important, causes of neuromuscular disease. Both result from the production of neurotoxins from clostridial species—*Clostridium botulinum* and *Clostridium tetani*, respectively.

Botulism

Botulism is an important differential for flaccid paralysis and is commonly mistaken for AIDP or MG. Botulinum toxin acts at the NMJ, preventing acetylcholine release. Botulism is characterized by progressive descending weakness, typically affecting the cranial nerves, without associated sensory involvement. In adults, the two main routes of exposure are ingestion of contaminated food and via wounds (including 'skin popping'). Diagnosis is by identification of toxin in serum or faeces. Wound swabs, faecal samples, and suspected food products should also be cultured for *C. botulinum* bacteria. Management should be undertaken in an ICU, as respiratory paralysis is common. Antibiotics (IV or IM benzylpenicillin 2.4–4.8g/day in divided doses every 6h; in penicillin-allergic patients, use IV metronidazole 500mg every 8h for 7 days), in addition to wound debridement, should be used in the management of wound-acquired botulism but avoided in food-borne disease due to concerns of bacterial cell rupture and release of more neurotoxin. In food-borne disease, laxatives, enemas, and, if caught early enough, gastric lavage have been tried to reduce gastrointestinal levels of neurotoxin. IV botulinum antitoxin should be administered as soon as possible.

Tetanus

Tetanus is caused by toxin secreted by wound-borne *C. tetani*, which binds peripheral nerve terminals and is subsequently transmitted to the CNS where it blocks the release of inhibitory neurotransmitters GABA and glycine. This results in spasms, commonly of the jaw (trismus), which may subsequently spread to other striated muscle groups, leading to sustained contraction. Autonomic dysfunction and respiratory failure occur in severe disease. Diagnosis is predominantly clinical, as wound culture for *C. tetani* has low sensitivity. Reported case fatality varies but can be as high as 80%. Treatment requires a combination of disease-specific therapy and supportive measures. The antitoxin and appropriate antibiotics, usually a combination of metronidazole and penicillin, should be administered as soon as possible. Adequate wound debridement is essential. Benzodiazepines ± magnesium sulfate are used to control muscle spasm, and sympathetic overactivity may require both α- and β-blockade.

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Chapter 16

Metabolic disorders

Introduction

Metabolic disorders with neurological involvement can be divided into three broad categories: inborn errors of metabolism, acquired nutritional deficiencies, and neuro-metabolic disorders due to toxins or drugs.

Inborn errors of metabolism

The conditions discussed in this chapter are those most commonly encountered in adult neurology practice and/or are amenable to specific treatments. A typical classification is given in Table 16.1.

Table 16.1 Neuro-anatomic classification of inherited neuro-metabolic disorders

Distribution of pathology	Disorders
Poliodystrophies (cortical grey matter: myoclonus, seizures, dementia, retinopathy)	Neuronal ceroid lipofuscinoses, GM2 gangliosidosis (Tay–Sachs), mucopolysaccharidoses (MPS), Gaucher's, Niemann–Pick
Leukodystrophies (white matter: spasticity ± ataxia, optic atrophy, cortical blindness, deafness)	Adrenoleukodystrophy (ALD), metachromatic leukodystrophy (MLD), Pelizaeus–Merzbacher, globoid cell dystrophy (Krabbe), phenylketonuria with dysmyelination
Corencephalopathies (deep telencephalon, diencephalon, and mesencephalon: movement disorders)	Wilson's disease, Huntington's disease
Spinocerebellopathies (spinal cord, cerebellum, pons, medulla: spasticity, ataxia)	Hereditary spastic paraplegias, Friedreich's ataxia, spinocerebellar ataxia (SCA), olivopontocerebellar atrophy
Diffuse encephalopathies	Hyperammonias, lactic acidaemias, homocysteinuria
Metabolic myopathies (muscle: rhabdomyolysis, exercise-induced myalgia, cramps, muscle weakness)	Acid maltase deficiency (Pompe), phosphofructokinase (PFK) deficiency, myophosphorylase deficiency (McArdle's)
Metabolic peripheral neuropathies (peripheral nerve: distal weakness and paraesthesiae)	Fabry disease, porphyria, SCA

Lysosomal storage disorders

In lysosomal storage disorders, deficiencies in specific enzymes cause the accumulation of non-degraded macromolecules within lysosomes that ultimately cause pathological changes to normal cell biology. The clinical phenotype of each disorder depends on which tissues have the highest turnover of accumulated macromolecule. To date, enzyme replacement therapy (ERT) has been approved worldwide for six lysosomal storage diseases: Gaucher's; Fabry; MPS types I, II, and VI; and Pompe disease.

Gaucher's disease

Gaucher's disease (glucosylceramide lipidosis) is the most prevalent of the lysosomal storage disorders, affecting 1 in 50 000 of the population worldwide, but 1 in 800 individuals of Ashkenazi Jewish descent. The primary metabolic defect is deficiency of glucocerebrosidase (also known as acid β-glucosidase), which leads to accumulation of glucocerebroside (glucosylceramide) within lysosomes. Lipid-laden macrophages, Gaucher's cells, are stored throughout the reticuloendothelial system and are useful in diagnosis. Diagnosis is confirmed by measurement of white cell glucocerebrosidase levels.

Several phenotypes are described. Type IIIA (chronic neuronopathic form) may present in adulthood with slowly progressive neurological deterioration, with the hallmark supranuclear horizontal gaze palsy, progressive myoclonic encephalopathy with seizures and dementia, and variable ataxia and spasticity.

Treatment

ERT with recombinant human glucocerebrosidase is effective for treating systemic manifestations, but the enzyme does not cross the blood–brain barrier, and there is no evidence that ERT reverses or slows the progression of neurological involvement. Haematopoietic stem cell transplantation may have a role in neuronopathic Gaucher's disease before neurological manifestations occur, and gene therapies are in development.

Fabry/Anderson–Fabry disease

Fabry disease is the commonest lysosomal storage disease, after Gaucher's disease, affecting ~1 in 100 000 of the population and 1 in 40 000 males. It is transmitted by X-linked recessive inheritance. Reduced activity of α-galactosidase A (α-Gal A) leads to accumulation of globotriaosylceramide in endothelial, vascular smooth muscle, and other cells, with multisystem consequences. The typical clinical picture is a 'bathing trunk' purpuric rash (angiokeratoma corporis diffusum) developing during childhood or adolescence. A painful sensory small-fibre peripheral neuropathy ± autonomic features is common in childhood or early adult life. Renal failure, strokes, cardiovascular disease, or hypertrophic cardiomyopathy can occur, generally by middle age. Life expectancy is typically reduced by 20 years.

Treatment

Management includes symptom relief for neuropathic pain, optimization of vascular risk factors, renal transplant for renal failure, and ERT.

Two different ERT products are available: Replagal® (agalsidase alfa) and Fabrazyme® (agalsidase beta).

Evidence base

Limited data are available on the effect of ERT on disease progression and survival. A meta-analysis of six studies showed that ERT did not prevent the development of cerebral white matter lesions but did reduce the rate of increase in left ventricular mass and risk of end-organ complications (stroke, cardiac or renal complications and death). The latest review from the Cochrane database concluded that, even though there is no robust evidence suggesting ERT provides prognostic benefits, it does have a significant effect on neuropathic pain.

Mucopolysaccharidoses

The MPS are a group of rare inherited disorders caused by specific lysosomal enzyme deficiencies, resulting in accumulation of incompletely degraded mucopolysaccharides in the cornea, cartilage, connective tissue, and reticuloendothelial system. There are seven subtypes, but all exhibit some period of normal development, followed by gradual decline of visceral, skeletal, and neurological function, the latter commonly including neurodevelopmental delay, cognitive and behavioural decline, seizures, sleep disorders, and optic neuropathy. There may also be high cervical cord compression from atlanto-axial instability and odontoid dysplasia, communicating hydrocephalus, and carpal tunnel syndrome. Diagnosis is made by detection of elevated urinary glycosaminoglycans (GAGs) and analysis of white cell enzymes.

Treatment

ERT is currently available for MPS types I, II, and VI. Haematopoietic stem cell transplantation has been used successfully in type I and is under investigation for the other types. Substrate reduction and gene therapies are in early development.

Acid maltase deficiency (Pompe)

An AR disease caused by deficiency of acid maltase (acid α-glucosidase), a lysosomal enzyme found in the CNS and skeletal muscle, which is involved in the conversion of maltose to glycogen. There are four clinical phenotypes, distinguished by age at onset: infantile, late infantile, juvenile, and adult. The later-onset forms present as motor developmental delay and/or progressive myopathy, often with prominent cardiorespiratory involvement. Visceromegaly is common in younger cases.

Treatment

ERT with alglucosidase alfa (Lymizyme® or Myozyme®) is effective, well tolerated, and attenuates progression. Two-thirds of patients stabilize or demonstrate improvement in CK levels and muscular and/or respiratory function on treatment.

Evidence base

The Late Onset Treatment Study (LOTS) demonstrated benefit of ERT in terms of walking speed and FVC, sustained for 104 weeks.

Peroxisomal disorders

Peroxisomes are cell organelles that are mainly involved in lipid metabolism and are responsible for the synthesis of β-oxidase very-long-chain fatty acids (VLCFAs), and play an important role in early myelination and neuronal migration.

X-linked adrenoleukodystrophy/adrenomyeloneuropathy

This is the commonest peroxisomal disorder, with an incidence between 1 in 20000 and 1 in 50000. Impaired activity of lignoceroyl-CoA ligase results in the accumulation of saturated VLCFA, resulting in severe inflammatory CNS demyelination. There is also adrenal gland and testicular atrophy.

There are four phenotypes: childhood cerebral X-ALD, adrenomyeloneuropathy (AMN), adolescent cerebral X-ALD, and adult cerebral X-ALD. Onset of AMN is usually in young adults, with slowly progressive spastic paraparesis and sphincter dysfunction, mild peripheral neuropathy, and subtle cognitive change. Up to 50% of female heterozygotes manifest a mild neurological syndrome resembling AMN. Diagnosis is made by detection of elevated serum VLCFA levels. Adrenal insufficiency is very common.

Treatment

Adrenal insufficiency should be treated with corticosteroid replacement. Early haematopoietic cell transplantation (HCT) can arrest the progression of, or even reverse, cerebral demyelination and is emerging as the treatment of choice for individuals with early stages of cerebral involvement in ALD. The mixture of oleic and eruric acid, known as Lorenzo's oil (LO), reduces the synthesis of VLCFAs by competitive inhibition of the enzyme responsible for elongation of saturated fatty acids. It normalizes plasma levels of VLCFA, but results of clinical studies are conflicting, and currently LO is recommended for presymptomatic ALD (without neurological symptoms or MRI abnormalities), but HCT should be offered early if neurological symptoms or MRI abnormalities develop. LO is also recommended for AMN and Addison's only phenotypes.

Refsum's disease

Refsum's disease is a rare AR peroxisomal disorder, in which abnormal fatty acid metabolism results in pathological accumulation of phytanic acid, a branched-chain fatty acid, in tissues, including myelin sheaths and internal organs. The onset of symptoms is usually during childhood or adolescence. Neurological manifestations include peripheral neuropathy, retinitis pigmentosa, cerebellar ataxia, sensorineuronal hearing loss, and anosmia. Clinical diagnosis is confirmed by elevated serum phytanic acid levels.

Treatment

Management involves dietary restriction of phytanic acid. When this is not sufficient, intermittent plasmapheresis targeting LDL- and very-low-density lipoprotein (VLDL)-bound phytanic acid results in long-term improvement or stabilization.

Wilson's disease

This is an AR-inherited condition in which mutations in the hepatic ATPase ATP7B result in reduced excretion of copper into bile and consequent gradual accumulation of copper in the liver, brain, and cornea.

Clinical manifestations are predominantly hepatic (18–84% at presentation), neurological (18–73%), and psychiatric (10–100%). Neurological manifestations usually occur in the teens or 20s and typically include dysarthria, dystonia, tremor, and/or parkinsonism. A common presentation is deterioration in handwriting and loss of fine motor control which may then progress to tremor, rigidity, and dysphagia with drooling. Deposition of copper in the cornea produces the Kayser–Fleischer (KF) rings seen on careful slit-lamp examination in 98% of individuals with neurological features of WD.

Diagnosis requires LFTs, FBC, serum caeruloplasmin and copper levels, 24h urinary copper excretion, and ocular slit-lamp examination to detect KF rings. Urinary copper excretion in response to a penicillamine (0.5g) challenge and liver biopsy with copper quantification may be necessary. Genetic confirmation of ATP7B mutations in the patient and siblings is recommended.

Treatment

Asymptomatic patients

- Initial treatment (duration ranges from 6 months to 5 years):
  - trientine 750–1500mg/day in two or three divided doses; or penicillamine 250–500mg/day, increasing by 250mg every 4–7 days to 1000–1500mg/day in two divided doses;
  - zinc 50mg tds if chelator not tolerated or declined.
- Adjunctive treatment: avoid copper-rich foods (shellfish, nuts, chocolate, mushrooms, organ meats), especially during year 1; pyridoxine 25–50mg daily (penicillamine inactivates pyridoxine).
- Maintenance (lifelong):
  - zinc 50mg tds or lower dose (approximately two-thirds initial dose) of chelating agent.

Symptomatic patients

- Initial treatment (duration ranges from 6 months to 5 years):
  - penicillamine 250–500mg/day, increasing by 250mg every 4–7 days to 1000–1500mg/day in two divided doses; or trientine 750–1500mg/day in two or three divided doses (although unlicensed, ammonium tetrathiomolybdate should be considered in patients with prominent neurological involvement, in light of its low incidence of initial neurological deterioration);
  - zinc 50mg tds can be added to chelating agent in severe disease.
- Adjunctive treatment as above.
- Maintenance (lifelong):
  - zinc 50mg tds or low (two-thirds) dose of chelating agent.

Acute liver failure or decompensated cirrhosis unresponsive to chelating agent

- Liver transplantation.

Routine monitoring

Serum copper and caeruloplasmin, LFTs, international normalized ratio (INR), FBC, and urinalysis at least 6-monthly. Annual 24h urinary copper excretion. Estimated serum non-caeruloplasmin-bound copper should be measured if non-adherence or over-treatment is suspected.

Untreated, WD is universally fatal, with the development of progressive cirrhosis, severe dystonia, and akinetic mutism. Prognosis for patients who adhere to treatment is excellent, even in some who already have advanced liver disease. Life expectancy is normal in patients without advanced liver disease, but treatment must not be discontinued. Treatment involves lowering copper levels with chelating agents. Penicillamine was the first agent used. Its use is limited by side effects in up to a quarter of patients, including early sensitivity reactions and late nephrotoxicity, bone marrow toxicity, and dermatological disorders. Trientine hydrochloride has better tolerability and similar efficacy. Both penicillamine and trientine can cause permanent neurological deterioration (in 2–22% and 10.5–26% of patients, respectively) during the initial phase of treatment. Zinc interferes with copper uptake from the gastrointestinal tract and promotes copper excretion through faeces by inducing metallothionein, an endogenous metal chelator. It is well tolerated and may have an increasing role in initial treatment in combination with penicillamine or trientine. Ammonium tetrathiomolybdate is a powerful chelating agent recently advocated for use in WD, although as yet unlicensed. It is particularly suitable for those with neurological involvement because of a considerably lower (~4%) incidence of neurological deterioration after treatment initiation, compared to penicillamine and trientine.

Evidence base

Guidelines for treatment include a 2008 consensus guideline from the American Association for the Study of Liver Diseases and a 2012 guideline from the European Association for the Study of the Liver.

Porphyria

The porphyrias are a group of disorders of haem synthesis, resulting in accumulation of porphyrin precursors aminolevulinic acid (ALA) and porphobilinogen (PBG) and of porphyrin intermediates uroporphyrin, coproporphyrin, and protoporphyrin. The AD-transmitted hepatic porphyrias have neuropsychiatric features. The commonest is acute intermittent porphyria (AIP), caused by a lack of PBG deaminase. Attacks of severe abdominal pain and vomiting, with diarrhoea or constipation and autonomic activation, commonly coincide with psychiatric features and sometimes seizures. In about half of cases, acute attacks are associated with a subacute axonal peripheral neuropathy. Attacks are precipitated by many commonly prescribed drugs (see websites of American Porphyria Foundation and European Porphyria Network for comprehensive and regularly updated lists), alcohol, reduced calorie intake, fluctuating sex hormones, stress, infection, smoking, and recreational drugs. Diagnosis is made by measuring urine PBG and porphyrins, and, if necessary, urine ALA and plasma and faecal porphyrins.

Treatment

Prompt diagnosis and treatment greatly improve prognosis and may prevent development of chronic neuropathic symptoms.

Supportive measures

1. **Eliminate precipitating factors.**
2. **Ensure optimal hydration and nutrition.**
3. **Treat symptoms with safe medications:**
   - pain: opiates (not pethidine);
   - vomiting: ondansetron or prochlorperazine;
   - agitation: chlorpromazine;
   - hypertension/tachycardia: beta-blockers;
   - seizures: clonazepam, diazepam, or magnesium sulfate.

Acute treatment of attacks

- First line: IV haematin 3–4mg/kg for 4 days.
- Second line: carbohydrate loading (IV glucose 300–500mg as 10% solution) only for attacks with mild pain and without severe manifestations.

Prophylaxis

- First line: avoid precipitating factors.
- Second line: regular haematin, gonadotrophin-releasing hormone (GnRH) analogue.
- Third line: liver transplantation.

IV haematin therapy, available in Europe as Normosang® (haemarginate) or in the USA as Panhematin® (lyophilized haematin), inhibits hepatic ALA synthetase and produces significantly improved outcomes when given early (within 24h of admission) in acute, severe attacks. Most attacks of acute porphyria should be treated promptly with IV haematin, certainly acute attacks associated with severe or prolonged pain, persistent vomiting, hyponatraemia, convulsions, psychosis, or neuropathy. Carbohydrate loading is only appropriate for mild attacks or until haematin becomes available, and haematin therapy should not be delayed because of ongoing carbohydrate loading.

The small proportion of AIP sufferers who develop recurrent attacks may benefit from prophylactic, regular haematin infusions, GnRH analogues, or liver transplantation.

Phenylketonuria

Phenylketonuria is the commonest of the inherited disorders of amino acid metabolism. Its inheritance is AR, and nearly all cases are due to the absence or mutation of the gene encoding hepatic phenylalanine hydroxylase (PAH), needed for the metabolism of phenylalanine into tyrosine. Large-scale screening programmes allow for diagnosis at birth. Another cause of hyperphenylalaninaemia (HPA) is tetrahydrobiopterin (BH4) deficiency. BH4 is a molecular chaperone for PAH, and its loss results in an impaired ability to convert phenylalanine to tyrosine. Untreated, HPA results in progressive psychomotor decline in the first decade of life. The predominant feature is intellectual disability, with impairment of IQ ranging from severe to moderate. Other neurological features include epilepsy and abnormalities of gait, sitting posture, and stance.

Treatment

- First line: a low phenylalanine amino acid diet.
- Second line: sapropterin dihydrochloride.

A low phenylalanine amino acid diet is the mainstay of management and prevents progressive psychomotor decline. Sapropterin dihydrochloride is a synthetic analogue of BH4.

Vitamin and nutrient deficiency syndromes

Vitamin deficiencies may occur as a result of inborn errors of metabolism, limited dietary intake, or failure of absorption. Several vitamin and micronutrient deficiencies have specific neurological manifestations (see Table 16.2). Malabsorption syndromes may cause multiple deficiencies, with resultant neurological dysfunction. Treatment of neurological deficiency syndromes is with replacement, which prevents progression and may or may not reverse established manifestations.

Table 16.2 Neurological deficiency syndromes

	Deficiency syndrome	Key features	Recommended dietary allowance (RDA) and replacement	Toxicity
Vitamin A	Night blindness, retinopathy, xerophthalmia, corneal ulceration, impaired immune function	Required for synthesis of retinal rhodopsin. Abundant in liver. Deficiency in fat malabsorption syndromes and malnourished	RDA 3000iu (= 900 micrograms retinol) male, 2300iu (= 700 micrograms retinol) female. Doses several fold higher than RDA recommended for fat malabsorption syndromes	Ataxia, alopecia, hyperlipidaemia, IIH bone and muscle pain, hepatotoxicity, teratogenicity
Vitamin B1 (thiamine)	Wernicke's encephalopathy (WE)—acute encephalopathy with ophthalmoplegia and ataxia Korsakoff's syndrome—chronic amnestic syndrome following WE Adult beriberi—distal axonal S-M neuropathy (dry) ± cardiomyopathy (wet)	Beriberi seen where there is high reliance on white rice, following weight loss surgery Chronic alcoholism reduces absorption	RDA 1.2mg male, 1.1mg female (1.4mg in pregnancy) WE—immediate 500mg IV thiamine over 30min tds for 2 days, then od for 5 days, then 100mg po od Beriberi—50–100mg IM or IV daily for 7–14 days	None. Excess is excreted in urine
Vitamin B3 (niacin, nicotinic acid)	Pellagra—'dementia, dermatitis, diarrhoea'. Hyperpigmented rash on sun-exposed areas, red tongue, anxiety, insomnia, disorientation, delusions, encephalopathy	Seen when there is over-reliance on dietary corn, in chronic alcoholics, after weight loss surgery, in anorexia nervosa. Also seen in carcinoid syndrome, prolonged isoniazid therapy, Hartnup disease	RDA 16mg (= 16 NE) male, 14mg (= 14 NE) female Used as lipid-lowering agent at high doses (1–3g daily)	Flushing High doses—nausea, vomiting, pruritus, constipation, elevated aminotransferases, myopathy, gout

(Continued)

Table 16.2 (*Contd.*)

	Deficiency syndrome	Key features	Recommended dietary allowance (RDA) and replacement	Toxicity
Vitamin B5 (pantothenic acid, coenzyme A)	Paraesthesiae/dysaesthesia of feet, 'burning feet syndrome'	Very rare outside famine	RDA 5mg	None. Excess is renally excreted
Vitamin B6 (pyridoxine)	Painful sensorimotor peripheral neuropathy, somnolence, confusion, glossitis, seborrhoeic dermatitis	Overt deficiencies rare. Deficiency usually due to drugs (isoniazid, hydralazine, penicillamine) or renal dialysis	RDA 1.3mg (1.7mg in >50 years, 1.9mg in pregnancy)	Ataxic peripheral neuropathy described with chronic intake of 100mg+ per day
Vitamin B12 (hydroxo-cobalamin)	Classically subacute combined degeneration of the cord (SACD)—progressive spastic paraparesis with sensory ataxia, peripheral neuropathy ± macrocytic anaemia. Also neuropsychiatric symptoms, cognitive impairment and depression, optic neuropathy	Pernicious anaemia, gastric and terminal ileum disorders, pancreatic insufficiency. Rare functional B12 deficiency due to abnormalities of transcobalamin proteins—high levels of precursors methylmalonic acid and homocysteine. Drugs blocking absorption include proton pump inhibitors, metformin, nitrous oxide anaesthesia. Vegan diet	RDA 6–9 micrograms Deficiency treated with IM vitamin B12 1mg daily for 1 week, then 1mg weekly for 4 weeks, then 1mg 1- to 3-monthly if underlying disorder persists	None. Excess excreted in urine

Vitamin D (calciferol)	Proximal myopathy Deficiency is associated with increased MS risk and worse disease course	Seen in hypoparathyroidism, chronic kidney disease, dietary deficiency, or inadequate exposure to sunlight	RDA 15–20 micrograms (600–800iu) colecalciferol (vitamin D3) Dose depends on nature and severity of deficiency Severe deficiency (serum 25-hydroxyvitamin D levels <20ng/mL or 50nmol/L)–50000iu once weekly or 20000iu once to twice weekly for 6–8 weeks, then maintenance1000–2000iu daily Insufficiency (20–30ng/mL or 50–75nmol/L)—1000–2000iu daily probably sufficient Malabsorption/gastrectomy may require 10000–50000iu daily, hydroxylated vitamin D metabolites (more readily absorbed), or sunlamp exposure	Hypercalcaemia/-uria, polydipsia/-uria, confusion, anorexia, vomiting, bone demineralization Upper limit 4000iu daily
Vitamin E (alpha-tocopherol)	Progressive ataxia, areflexia and distal axonal neuropathy, neuromuscular disorders, haemolysis	Deficiency in fat malabsorption syndromes (abetalipoproteinaemia, cystic fibrosis, coeliac disease, cholestasis)	RDA 15mg (= 22iu natural or 33iu synthetic vitamin E). Fat malabsorption syndromes—25–50mg od	? increased risk of bleeding

(Continued)

Table 16.2 *(Contd.)*

	Deficiency syndrome	Key features	Recommended dietary allowance (RDA) and replacement	Toxicity
Copper	Myelopathy mimicking B12 deficiency, SACD, peripheral neuropathy, bilateral optic neuropathy, usually with anaemia and leucopenia	After gastric surgery, prolonged total parenteral nutrition, excess zinc ingestion (competes for copper absorption in jejunum), enteropathies with malabsorption	RDA 900 micrograms. Deficiency—elemental copper 2mg daily. Higher doses (8mg daily, reducing by 2mg every week to 2mg) or IV doses may be required for severe symptoms initially. Zinc discontinued if relevant	Gastrointestinal symptoms, cardiac and renal failure, hepatic necrosis, encephalopathy Upper limit 10mg daily
Selenium	Proximal myopathy and painful myalgia, cardiomyopathy	Rare. Linked with regional low soil selenium levels (e.g. in China)	RDA 55 micrograms	Gastrointestinal symptoms, hair and nail loss, encephalopathy, peripheral neuropathy Upper limit 400 micrograms daily
Strachan's syndrome	Painful polyneuropathy, sensory ataxia, optic neuropathy, hearing loss, mucocutaneous lesions	Initially described in malnourished in Jamaica and in prisoners of war (Jamaican neuritis, Cuban epidemic neuropathy). Due to multivitamin deficiency, particularly B vitamins	Early treatment with vitamin B and multivitamin preparations may resolve neuropathy > optic neuropathy	n/a

Neurological toxicity syndromes

The nervous system is susceptible to damage from a wide variety of environmental agents. Exposure may be deliberate or accidental and can occur via ingestion, inhalation, or absorption through the skin or mucous membranes. Table 16.3 includes the more commonly encountered neurotoxins, their typical neurological syndromes, and available treatment options.

Table 16.3 Treatable neurological toxicity syndromes

	Toxicity syndrome	Key features	Treatment
Alcohol	Acute intoxication and withdrawal, seizures, WE, Korsakoff's syndrome (thiamine deficiency), central and extrapontine myelinolysis, Marchiafava–Bignami disease, hepatic encephalopathy Chronic complications—cognitive impairment, cerebellar atrophy, seizures, peripheral neuropathy	No single cause of alcohol-related brain damage—as well as Korsakoff's syndrome, repeated episodes of intoxication and withdrawal, dietary neglect, vitamin deficiencies, traumatic brain injury, cerebrovascular event, and alcoholic liver disease may contribute	Abstinence, adequate nutrition Thiamine 100mg od (see thiamine deficiency)
Lead	In adults, symmetrical pure motor polyneuropathy (upper > lower limbs), with prominent gastrointestinal disturbance. Blue line at gingival margin. Acute encephalopathy in children High CSF pressure, protein, and cells; basophilic stippling of marrow normoblasts. High blood lead levels, urine coproporphyrins	Commonest cause of heavy metal intoxication. Common sources include lead paint, water from lead pipes, burning or melting lead, and leaded gasoline	Eliminate exposure Chelation treatment with calcium EDTA, dimercaprol (British Anti-Lewisite—BAL) 3–5mg/kg IM 4- to 6-hourly, or penicillamine 500mg 6-hourly for 5 days Early treatment can improve neuropathy. Mannitol for raised ICP
Mercury	CNS toxicity—intention tremor, ataxia, sensory neuropathy, personality change, agitation, perioral paraesthesiae, progressive encephalopathy, visual field constriction, coma, and death Pneumonitis, inflamed gums, hypersalivation. Nephrotoxicity. Confirmed by high mercury levels in blood (>100 micrograms/L—normal <5 micrograms/L) and urine	Exists in metallic, inorganic, and organic forms (methylmercury in contaminated fish). Used in production of thermometers, mirrors, and latex paints, gold mining, and present in amalgam fillings (the latter not associated with toxicity). Metallic and organic forms are toxic to CNS; inorganic forms may be nephrotoxic. Exposure can be via inhalation of vapour, ingestion, or cutaneous absorption	Eliminate/limit exposure For CNS toxicity, prompt chelation with penicillamine 500mg 6-hourly for 5 days, DMSA (dimercaptosuccinic acid) 10mg/kg 8-hourly for 5 days, or dimercaprol (BAL) 3–5mg/kg IM 4- to 6-hourly

Arsenic	Distal painful sensorimotor axonal neuropathy following acute poisoning or progressive with chronic exposure. Hyperpigmentation (dermatitis, jaundice) and autonomic involvement. Occasional encephalopathy. Mees' lines on nails in chronic exposure	Odourless, tasteless, highly toxic. Herbicides and pesticides, rodenticides, illicit alcohol, well water Blood, urine, hair, and nail arsenic levels	Acute poisoning—decontaminate skin, activated charcoal if recent ingestion (<1h), and supportive care Chelation with dimercaprol/BAL (3–5mg/kg IM 4- to 6-hourly), DMSA, or unithiol (DMPS—2,3-dimercapto-1-propane sulfonate) until 24h urinary arsenic <50 micrograms/L
Manganese	Progressive encephalopathy ('manganese madness') with fatigue, apathy, insomnia, hallucinations, and personality change Chronic exposure may lead to extrapyramidal features—parkinsonism with dystonia, neuropathy	Ubiquitous in living organisms and serves as an enzyme cofactor. Sources of toxicity include industrial exposure in iron and steel manufacturing and welding, and occasionally well water and total parenteral nutrition	Chelation with EDTA may help Levodopa
Methanol and ethylene glycol	Lethargy, progressive hypersomnolence, coma, seizures, visual loss (methanol), flank pain and haematuria, renal toxicity (ethylene glycol), and profound metabolic acidosis	Present in antifreeze and de-icing solutions, windshield wiper fluid, solvents. Ingestion can occur deliberately when used as ethanol substitute, accidentally, by consumption of illicitly distilled alcohol (moonshine), deliberate self-harm	Block alcohol dehydrogenase with fomepizole15mg/kg IV, then 10mg/kg 12-hourly. Ethanol used if fomepizole not available. Haemodialysis, IV sodium bicarbonate

(Continued)

Table 16.3 (*Contd.*)

	Toxicity syndrome	Key features	Treatment
Organo-phosphates	Acute cholinergic toxicity—salivation, lacrimation, mydriasis, bronchospasm, diarrhoea, urination, fasciculation, muscle weakness, central respiratory depression, coma, seizures Intermediate neurological syndrome in 40% after 1–3 days—diffuse muscle weakness (limb, bulbar, respiratory muscles), areflexia, cranial neuropathies Delayed neurotoxicity—painful distal paraesthesiae, followed by distal motor neuropathy	Used in pesticides and exposure common in agricultural settings. Inhibit acetylcholinesterase	Supportive care, ventilation, 100% oxygen Cholinergic symptoms—atropine 2–5mg IV bolus, repeated as necessary Pralidoxime 30mg/kg IV bolus over 30min for cholinergic symptoms and neuromuscular dysfunction Benzodiazepines for seizures
Carbon monoxide	Constitutional symptoms, headache, dizziness, alterations in mental state ranging from mild confusion to coma and seizures Elevated serum carboxyhaemoglobin level Late neurocognitive deficits in up to 40%—cognitive and personality change, parkinsonism, other focal deficits	Clear, colourless, odourless gas. Poisoning from inadvertent or deliberate smoke inhalation, heating system dysfunction, poorly ventilated fuel burning devices, motor exhaust	Immediate 100% oxygen via non-rebreathing face mask Consider hyperbaric oxygen for severe intoxication
Cyanide	Acute poisoning—headache, confusion progressing to seizures and coma. Cardiovascular dysfunction, cherry red flushing Delayed-onset parkinsonism Chronic exposure—tobacco–alcohol amblyopia, tropical ataxic neuropathy (TAN) Konzo (acute non-progressive spastic paraparesis)	Fire, industrial exposure (plastics and rubber production, pesticides, fertilizer, metallurgy) Konzo and TAN—reliance on underprocessed cassava during famine. Cassava contains high levels of cyanogens and few sulfur-containing amino acids	Hydroxycobalamin 5g IV stat If not available, use 'Cyanide Antidote Kit' (only after carbon monoxide poisoning excluded)—25% sodium thiosulfate 1.65mL/kg IV plus amyl nitrite inhaled for 30min every minute plus sodium nitrite 10mg/kg IV

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Chapter 17

Uro-neurology

Introduction

Urinary and sexual symptoms associated with neurological disease have a tremendous impact on a patient's quality of life and are common in disorders such as MS, extrapyramidal disorders, spinal cord dysfunction, and dementia.

Two broad categories of neurogenic bladder dysfunction occur, depending, to an extent, on the site of the neurological lesion(s). These are detrusor overactivity and voiding dysfunction. These can occur individually or in combination. Appreciation of this is essential for successful tailoring of therapies. For example, patients with MS not uncommonly have symptoms of urinary urgency, micturition frequency, urge incontinence, and voiding difficulties, due to a combination of detrusor overactivity and incomplete bladder emptying from detrusor–sphincter dyssynergia. Hence, treatment of detrusor overactivity in these circumstances can worsen incomplete bladder emptying.

This chapter outlines the management of urogenital dysfunction of neurological origin and specifically covers overactive bladder, non-obstructive urinary retention, and erectile dysfunction.

Neurogenic lower urinary tract dysfunction

History taking and a bladder diary form the cornerstone of assessment of the patient with suspected neurological urinary dysfunction. Urine dipstick testing is important to rule out infection, and post-micturition bladder ultrasound to detect incomplete bladder emptying is often useful, as 50% of patients are unaware of incomplete voiding. Additionally, urodynamic testing can help to clarify the pattern of lower urinary tract dysfunction.

Overactive bladder

The commonest type of neurogenic lower urinary tract dysfunction is an OAB, also referred to as detrusor overactivity or detrusor instability. Typical symptoms include urinary urgency and frequency, nocturia, and urge incontinence. Detrusor overactivity can also be demonstrated in urodynamic studies. An OAB occurs as a result of lesions of the spinal cord or suprapontine pathways. Typical causes include spinal cord injury, MS, cerebrovascular disease, dementia, and extrapyramidal disorders, e.g. PD.

Treatment

All patients should be given advice to avoid exacerbating factors, i.e. to limit fluid intake to the recommended 1.5–2L/day and to avoid caffeinated drinks and alcohol. In addition to these, therapies used to treat the underlying disease may help to address urinary symptoms.

Pharmacological

- First line: antimuscarinic medications (see Table 17.1).
- Second line: β3-adrenoceptor agonists (mirabegron) or desmopressin.
- Third line: intravesicular botulinum toxin.

Neuromodulation

1. Percutaneous tibial nerve stimulation (PTNS).
2. Sacral neuromodulation.

Surgical

1. Augmentation cystoplasty.
2. Urinary diversion.

Evidence base

1. *Antimuscarinic agents*: these are very effective drugs, typically used first-line for OAB symptoms. Meta-analyses have demonstrated there are no major differences in efficacy between the different agents, and they share a similar side effect profile, which includes central effects such as dry mouth and cognitive impairment. Individual variations relate to their muscarinic receptor selectivity, pharmacokinetics, and metabolism (see Table 17.1). Importantly, antimuscarinics may worsen the efficiency of bladder emptying so should be used with caution in those with mixed OAB and incomplete bladder emptying.
2. *Desmopressin*: a synthetic form of the antidiuretic hormone (ADH) vasopressin, which works by temporarily reducing urine production by promoting reabsorption of water by the renal collecting ducts. It can be effective for troublesome nocturia associated with OAB not responsive to antimuscarinics, but its use is limited by side effects of hyponatraemia, fluid retention, and seizures. One RCT demonstrated that 34% of patients with OAB had the number of nocturia episodes halved with desmopressin, compared to 3% with placebo.

Table 17.1 Antimuscarinic medications

Generic	Dose (mg)	Frequency	Receptor subtype	Elimination half-life (h)
Tolterodine	2 (4)	bd (od)	Non-selective	2.4 (8.4)
Trospium	20	bd	Non-selective	20
Oxybutynin	2.5–5	bd to qds od	Non-selective	2.3
Oxybutynin XL	5–30	bd to qds od	Non-selective	13.2
Propiverine	15	od to qds	Non-selective	4.1
Darifenacin	7.5–15	od	Selective M3	3.1
Solifenacin	5–10	od	Selective M2 plus M3	40–68
Propantheline	15	tds	Non-selective	<2
Fesoterodine	4–8	od	Non-selective	7

bd, twice daily; od, once daily; qds, four times daily.

3. *Mirabegron*: this is the first of a new class of drugs for OAB. It is a β3-adrenergic receptor agonist that induces direct relaxation of the detrusor smooth muscle. Two phase 2 and five phase 3 RCTs show that mirabegron is efficacious and appears to be well tolerated in the treatment of OAB (see drug monograph Mirabegron, pp. 529–31).
4. *BTX-A*: cystoscopy-guided botulinum toxin injections into the detrusor muscle significantly improves urinary urgency, incontinence, bladder capacity, and detrusor pressures in patients with OAB. The beneficial effect of each procedure lasts for ~8–11 months. Up to 40% of patients need to perform intermittent self-catheterization (ISC), following botulinum toxin injection (compared to 10% at baseline); hence, patients should be made aware of this, prior to treatment. In one RCT, onabotulinum toxin A reduced mean incontinence by 23 episodes per week, compared to nine episodes per week in the placebo group (p <0.001). Quality of life scores were also significantly improved.

Neuromodulation

This most commonly involves PTNS or sacral neuromodulation. The mechanism by which these techniques work is unknown. PTNS is a minimally invasive technique involving electrical stimulation of the posterior tibial nerve with a fine-gauge needle.

Sacral neuromodulation is a two-stage surgical procedure whereby the S3 nerve root is electrically stimulated. It has been shown to be

beneficial in treating detrusor overactivity/urge incontinence, as well as non-obstructive urinary retention.

Evidence base

Sacral neuromodulation has been studied in a small number of neurological patients and has shown benefit in patients with MS. In patients with early spinal cord injury, it can reduce bladder pressures and prevent the development of detrusor overactivity, when compared to controls. In a double-blind, randomized-controlled study comparing 12 weeks of PTNS to a sham treatment, 55% of patients had response to treatment, compared to 21% of the control group (p <0.001).

Non-obstructive urinary retention

Urinary retention may occur in the context of neurological disease affecting the spinal or infraspinal pathways. When it occurs in the context of spinal cord disease, it is usually due to incoordination of detrusor and sphincter contraction and relaxation (detrusor–sphincter dyssynergia). Incomplete bladder emptying arising from lesions of infraspinal pathways is usually because of poorly sustained detrusor contractions ± non-relaxation of the sphincters. Causes include lesions of the conus medullaris, cauda equina, lumbosacral roots, and less commonly peripheral nerves. Spina bifida and MS commonly cause a mixture of OAB and incomplete bladder emptying.

Treatment

Compared to OAB, there are fewer management options for patients with urinary retention.

- First line: catheterization is the mainstay of management. Patients may opt for intermittent catheterization or an indwelling urethral or suprapubic (preferable) long-term catheter.
- Second line: sacral neuromodulation is useful in some patients with chronic non-obstructive urinary retention, especially with a primary disorder of urethral sphincter relaxation (Fowler's syndrome).

Evidence base

Catheterization has been demonstrated to reduce deterioration of kidney function in patients with urinary retention after spinal cord injury. However, potential side effects include urinary tract infection and trauma. With regards sacral neuromodulation, one systematic review of 14 studies (one RCT and 13 observational studies), the mean difference in post-void residual decreased by 236mL (p <0.0001), and voided volume increased by 299mL (p <0.0001), suggesting that this is a highly effective treatment. However, there is a high complication rate, with 53% needing surgical revision of their implant at some point.

Disorders of sexual function

Sexual function is a complex neurovascular process. Only disorders of male sexual function will be discussed in this section.

Erectile dysfunction

Neurological conditions, such as traumatic brain injury, stroke, spinal cord injury, MS, PD, MSA, and epilepsy, can predispose an individual to erectile dysfunction. However, it can often be multifactorial, and the common causes, such as depression, antidepressant use, diabetes, β-blockers, and peripheral vascular disease, must be ruled out first.

Treatment

Factors that influence sexual function in patients should be addressed individually. Treatments range from psychological therapies to pelvic floor exercises, medication, and local interventions.

- First line: phosphodiesterase 5 (PDE5) inhibitors are effective in treating erectile dysfunction of neurological origin. There are various formulations with variable potency, including sildenafil, tadalafil, and vardenafil.
- Second line: vacuum constriction devices.
- Third line: intracavernous prostaglandin E2 injections.

Evidence base

All three PDE5 inhibitors have statistically similar efficacy and safety profiles. The commonest side effects are headache and flushing. One RCT of sildenafil for erectile dysfunction in patients with MS demonstrated significantly increased erectile function scores, compared to placebo (p <0.001). Vacuum constriction devices can improve erections and sexual intercourse in up to 80% of patients in one retrospective study; however, trials have demonstrated a dropout rate of around 30%, due to complaints of bruising, pain, and numbness of the penis. Intracavernous injections have a similar efficacy rate in patients but have a higher dropout rate, due to the continued use of needles which lends itself to complications.

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Chapter 18

Drugs causing neurological disease

Drugs causing neurological disease

Listed below are medications known to cause or aggravate neurological disease. Drugs causing parkinsonism and MG are listed in their respective chapters.

Cerebellar syndrome

- Aminoglycosides (e.g. gentamicin).
- Amiodarone.
- Barbiturates (e.g. phenobarbital).
- Carbamazepine.
- Cytarabine.
- Fluorouracil.
- Lithium.
- Phenytoin.
- Piperazine.

Chorea

- Amiodarone.
- Amphetamines.
- Antihistamines.
- Antipsychotics.
- Levodopa (associated dyskinesias).
- Metoclopramide.
- Oral contraceptives.
- Phenytoin with lamotrigine.

Dystonia

- Antidopaminergic agents (causing tardive dyskinesias, e.g. tetrabenazine, reserpine, antipsychotics).
- Antihistamines.
- Antiemetics (domperidone, metoclopramide, and prochlorperazine).
- Antimalarials (e.g. chloroquine).
- Phenytoin.
- Phenobarbital.

Myoclonus

- Anticonvulsants (e.g. gabapentin, pregabalin, lamotrigine, phenytoin, phenobarbital).
- Antidepressants.
- Antidiarrhoeal (bismuth subsalicylate).
- Benzodiazepines.

- Calcium channel blockers.
- Cephalosporin antibiotics (e.g. ceftazidime).
- Clozapine.
- Contrast media.
- Levodopa.
- Lithium.
- Opioids (e.g. morphine).
- Propofol.
- Quinolone antibiotics (e.g. ciprofloxacin).

Myopathy

- Aminocaproic acid.
- Amiodarone.
- Antimalarials—chloroquine, hydroxychloroquine.
- Colchicine.
- Emetine (in ipecac).
- Etretinate.
- Glucocorticoids—especially 9-α-fluorinated (dexamethasone, betamethasone, triamcinolone).
- Lipid-lowering drugs—statins, fibrates, nicotinic acid, ezetimibe.
- Penicillamine (myositis).
- Perhexiline.
- Recreational drugs—alcohol, cocaine.
- Streptokinase.
- Vincristine.
- Zidovudine (inhibits mitochondrial DNA replication).

Peripheral neuropathy

- Amiodarone.
- Antibacterials—metronidazole, misonidazole, nitrofurantoin, ethambutol.
- Antineoplastic agents—vincristine, adriamycin, taxanes (paclitaxel, docetaxel).
- Antirheumatics—gold, chloroquine (plus myopathy).
- Bortezomib.
- Dapsone.
- Disulfiram.
- HAART—zalcitabine, didanosine, stavudine.
- Nitrous oxide (plus myelopathy).
- Phenytoin.
- Pyridoxine.
- Suramin.
- Thalidomide.

Posterior reversible encephalopathy syndrome (PRES)

- Anti-angiogenic agents (e.g. bevacizumab).
- Antiretroviral (e.g. indinavir).
- Chemotherapy (e.g. cisplatin, gemcitabine, methotrexate, vincristine).
- Cocaine.
- Immunosuppressive agents (e.g. tacrolimus, ciclosporin).
- IV immunoglobulins:
  - monoclonal antibodies (e.g. rituximab).

Seizures

- AChEIs (e.g. donepezil, memantine, rivastigmine).
- Antibacterials (e.g. cephalosporins, quinolones, fluoroquinolone).
- Anticholinergics (e.g. tolterodine, oxybutynin, trihexyphenidyl).
- Antifungals (e.g. amphotericin B).
- Antiretrovirals (e.g. efavirenz, zidovudine).
- Antivirals (e.g. aciclovir, ganciclovir).
- Baclofen (withdrawal).
- Benzodiazepines (withdrawal).
- Chemotherapy (e.g. busulfan, cisplatin, methotrexate, vincristine).
- Immunomodulators (e.g. ciclosporin, mycophenolate, prednisolone, tacrolimus).
- Isoniazid.
- Methylphenidate.
- Recreational (alcohol, cocaine, amphetamines).

Tics

- Cocaine.

Tremor

- Amiodarone.
- Antidepressants.
- Sodium valproate.
- Sympathomimetics (e.g. bronchodilators, theophylline, pseudoephedrine).

Section 2

A–Z index of neurological drugs

Chapter 19

A–Z index of neurological drugs

Drug classes

Individual drugs

Acetylcholinesterase inhibitors

AChEIs, also known as cholinesterase inhibitors or anticholinesterases, are a large group of drugs that bind to and inhibit cholinesterase, thereby elevating levels of acetylcholine within the synaptic cleft. Only reversible AChEIs are used therapeutically, as irreversible AChEIs are highly toxic and used as insecticides or in chemical warfare. Reversible AChEIs are used in the symptomatic management of NMJ disorders and dementia, most commonly AD.

Three cholinesterase inhibitors are used for the treatment of NMJ pathology. These are edrophonium, neostigmine, and pyridostigmine. Pyridostigmine is the most widely used AChEIs for this indication, as it has a longer duration of action and superior side effect profile. Edrophonium and neostigmine have shorter durations of activity. Edrophonium, in particular, has such a short half-life that it is predominantly used as a diagnostic test for MG (the Tensilon® test). Neostigmine is four times as potent as pyridostigmine and hence has more pronounced cholinergic side effects.

Reversible AChEIs which cross the blood–brain barrier include donepezil, galantamine, and rivastigmine. These medications are licensed for use in the treatment of mild to moderate AD. They differ in terms of their pharmacokinetics, their specificity for acetylcholinesterase, and their affinity for acetylcholinesterase in different parts of the CNS. This may contribute to differences in their efficacy and side effect profiles. The advantages and disadvantages of different AChEIs used in dementia are given in Table A.1.

Table A.1 A comparison of AChEIs used in the treatment of dementia

	Preparations	Advantages	Disadvantages
Donepezil	Orodispersible and standard tablet. Donepezil is also available as a solution	Renal impairment is not a contraindication; beneficial effects on behaviour; orodispersible formulation aids compliance	Potential for drug interactions by CYP450 enzyme inhibitors/ inducers
Galantamine	Oral solution, prolonged-release capsules and tablets, and standard tablets	Prolonged-release versions allow od dosing. Least expensive treatment for AD	Cautionary use in hepatic impairment and potential for drug interactions by CYP450 enzyme inhibitors or inducers
Rivastigmine	Capsules, oral solution, and patch	Available as a patch, no interaction with CYP450 enzyme inhibitors/ inducers, beneficial effects on behavior, and licensed in PDD (and DLB in UK)	May be associated with more gastrointestinal side effects than donepezil

Mechanism of action

- *NMJ disorders*: reversible inhibition of cholinesterase serves to increase synaptic concentrations of acetylcholine, potentiating the action of acetylcholine on muscarinic and nicotinic AChRs. The former group of receptors contribute to the side effect profile, and the latter to the therapeutic effect.
- *Dementia*: AChEIs were initially developed on the basis of the 'cholinergic hypothesis', i.e. post-mortem studies of the brains of patients with AD were found to be deficient in acetylcholine. In light of increased knowledge of the pathology of AD, this is now felt to be an oversimplification. AChEIs are thought to exert their beneficial effects in a number of ways, including activation of neurotrophic mechanisms, modulation of amyloid plaque and neurofibrillary tangle synthesis, and potential protection of the brain from glutamate-induced excitotoxicity. In addition to anticholinesterase activity, donepezil independently interacts with neuronal nicotinic AChR; rivastigmine forms temporary covalent bonds with the AChR, and galantamine may enhance the intrinsic action of acetylcholine on nicotinic receptors. The clinical significance of these variations in activity profile is unclear.

Toxicity and side effects

Side effects shared by all cholinesterase inhibitors

- *Common—gastrointestinal*: abdominal cramps, diarrhoea, dyspepsia, increased salivation, nausea, vomiting, and weight loss.
  Urological: incontinence.
- *Serious—cardiovascular*: arrhythmias, bradycardia, heart block, hypotension, and syncope.

Side effects shared by donepezil, galantamine, and rivastigmine

- *Common—musculoskeletal*: arthralgia and muscle cramps.
  Neurological: dizziness, fatigue, headache, insomnia, and weakness.
  Psychiatric: abnormal dreams, agitation, depression, and hallucinations.
- *Serious—gastrointestinal*: hepatitis and gastric/duodenal ulcers.
  Haematological: anaemia and thrombocytopenia with galantamine.
  Neurological: seizures and worsening of symptoms of PD. NMS has been reported with donepezil and rivastigmine use.

Side effects shared by edrophonium, neostigmine, and pyridostigmine

- *Serious—neurological*: paralysis and weakness.
  Respiratory: bronchoconstriction and increased bronchial secretions.
- *Cholinergic crisis*: with overdose, there is a risk of cholinergic crisis developing as a result of a depolarizing neuromuscular blockade. This can cause potentially lethal bulbar and respiratory muscle weakness. It is important to distinguish this from a worsening myasthenic crisis, as management is very different.

Contraindications

Contraindications shared by all acetylcholinesterase inhibitors

- *Absolute*: hypersensitivity to the individual drug or its excipients. AChEIs should not be given to patients with mechanical intestinal or urinary obstruction.

- *Relative*: caution is advised in patients with asthma and chronic obstructive pulmonary disease (COPD), co-morbid bradycardia, arrhythmia, sick sinus syndrome, peptic ulcer disease, epilepsy, and parkinsonism.

Contraindications shared by edrophonium, neostigmine, and pyridostigmine
Hyperthyroidism and recent coronary artery occlusion. In patients with chronic kidney disease, elimination of AChEI may be prolonged; hence dose reduction may be required. No dose alteration is required in hepatic failure.

Efficacy

Central acetylcholinesterase inhibitors for dementia

- *Donepezil*: a 2006 Cochrane review of donepezil use in AD (n = 5769, from 24 RCTs) concluded that cognition, assessed with the ADAS-Cog scale, improved with donepezil use at 24 weeks. For 5mg and 10mg doses, there was an improvement of −2.01 points mean difference (95% CI −2.69 to −1.34; p <0.00001) and −2.80 points mean difference (95% CI −3.74 to −2.10; p <0.0001), respectively, compared with placebo. The study also concluded that there was a non-significant improvement of 1.84 points in the MMSE score at 52 weeks, when compared to placebo (95% CI 0.53–3.15; p = 0.006). Studies suggest that there is marked inter-patient variability in patients' response to donepezil. However, there are as yet no indicators to suggest the extent of response in individual patients.

  Evidence from open-label extension trials of up to 3 years suggests that the rate of cognitive decline in treated patients may be less than that of untreated patients. In addition, donepezil has also been shown to reduce non-cognitive features of AD, such as low mood, hallucinations, and delusions, in mild to moderate disease. A trial of 10mg vs 23mg donepezil in patients with moderate-severe AD did not show a significant difference in global functioning. Although post-hoc analyses have suggested some benefit in more severe AD, for some of the ratings scales used (see p. 267). Patients taking the higher dose developed a higher incidence of dizziness and GI side effects.
- *Galantamine*: a 2014 meta-analysis of three placebo-controlled trials of galantamine in patients with mild to moderate AD showed a pooled weighted mean difference (WMD) in change between intervention and placebo of −3.03 (95% CI −3.66 to −2.41) and −3.2 points (95% CI −3.28 to −3.12) in the ADAS-Cog score at 24mg and 32mg doses of galantamine, respectively. Current head-to-head trials have not shown a difference between galantamine and donepezil. Adjusted indirect comparison studies suggest that non-cognitive features, such as behaviour, respond better to donepezil and rivastigmine than galantamine, and that, in general, galantamine is less well tolerated than the other AChEIs.
- *Rivastigmine*: in 2009, the Cochrane collaboration systematically reviewed the use of rivastigmine in mild to moderate AD. They included nine double-blind, placebo-controlled, randomized trials of 4775 patients receiving 6–12mg of rivastigmine and showed a 2-point improvement in cognitive function on the ADAS-cog score vs placebo (WMD −1.99, 95% CI −2.49 to −1.50; p <0.00001) on an intention-to-treat basis at 26 weeks. A 2.2-point improvement in the activities of

daily living, assessed on the Progressive Deterioration Scale, was also seen (WMD −2.15, 95% CI −3.16 to −1.13).

In severe AD, several randomized, placebo-controlled trials showed reduction in cognitive decline in moderately severe (Geriatric Depression Scale (GDS) less than or equal to 5) AD. Mean change from baseline ADAS-Cog scores was significantly improved in patients receiving 6–12mg/day of rivastigmine (2.3, 95% CI 0.09–3.84; p <0.001) and 1–4mg/day of rivastigmine (−1.2, 95% CI −2.61 to 0.31; p <0.001) at 26 weeks in one placebo-controlled trial of 159 patients.

A 2012 Cochrane review assessed the use of AChEIs in PDD and DLB (1236 participants in six randomized, placebo-controlled trials). An improvement in cognitive function, as measured by MMSE scores, was noted for PDD (mean difference 1.09, 95% CI 0.45–1.73; p = 0.0008), but not for DLB. In PDD, cholinesterase inhibitors were also demonstrated to have a positive effect on behavioural assessment and activities of daily living, with no significant impact on Unified Parkinson's Disease Rating Scale (UPDRS) scores. The Cochrane review concluded that the effects in DLB remained unclear.

Peripheral acetylcholinesterase inhibitors for neuromuscular junction disorders

- *Edrophonium*: the edrophonium test for diagnosing MG is positive if a substantial improvement in muscle power occurs in an objectively visible muscle group, most commonly interpreted by resolution of ptosis. The test has a sensitivity of 95% for generalized MG, although a variety of neuromuscular disorders, such as LEMS, can yield a false-positive result.
- *Neostigmine*: there have been no good-quality RCTs regarding the use of neostigmine in MG, other than one small and inconclusive trial using intranasal neostigmine in ten participants. Nonetheless, there is a wealth of clinical observational experience which points to the efficacy of neostigmine in treating MG. Its side effect profile and relatively short duration of action means it is less widely employed than pyridostigmine for this purpose.
- *Pyridostigmine*: although there are no randomized, placebo-controlled trials of the use of oral pyridostigmine in the treatment of MG, there is a wealth of clinical observational evidence which points to its efficacy. As such, guidelines state that pyridostigmine is the first-line treatment for all forms of MG, with the caveat that patients with anti-MuSK antibodies likely have a reduced benefit when compared to ACRA positive patients.

Dosing and monitoring

Central acetylcholinesterase inhibitors for dementia

- *Donepezil*: start treatment at 5mg od at night. This can be increased to 10mg after 4–6 weeks. The 23mg dose (available in the USA, not UK) can be administered to patients with severe AD, once patients have been established on 10mg for at least 3 months.
- *Galantamine*: for oral solution and standard tablets, start treatment at 4mg bd, increasing to 8mg bd after 4 weeks. This can again be increased

to 12mg bd after a further 4 weeks, depending on individual tolerability. For extended-release preparations, start treatment at 8mg od dose, taken in the morning with food. Increase to 16mg after 4 weeks and, if tolerated, 24mg after a further 4 weeks.

- *Rivastigmine*: for oral rivastigmine, start treatment at 1.5mg bd. This can be increased by 1.5mg/dose every 2 weeks to a maximum of 6mg bd.
  - For transdermal preparations, start treatment with a 4.6mg/24h patch applied od and increasing to 9.5mg/24h patch after a minimum of 4 weeks. If well tolerated and there is evidence of benefit, this can be further increased to 13.3mg/24h after 6 months. When dosing is omitted for >3 days, reinitiation at the lowest dose is recommended.
- *Monitoring of central AChEIs for dementia*: activities of daily living, behaviour, cognitive function, and mood should be monitored during treatment.

Peripheral acetylcholinesterase inhibitors for neuromuscular junction disorders

- *Edrophonium*:
  - *diagnosis of MG*: a test dose of 2mg IV is administered over 15–30s. If no reaction is noted after 60s, an 8mg bolus is given into a large IV line, followed by a saline flush. If cannulation is unsuitable or unsafe, 10mg IM can be given as an alternative. Oral cholinesterase inhibitors should be withheld for 24h prior to testing;
  - *assessment of treatment adequacy of MG*: a test dose of 2mg IV is administered >1h after the last administration of the patient's usual pyridostigmine dose. If the patient has been over-treated with pyridostigmine, administration of edrophonium will transiently worsen symptoms; conversely, if the patient has been receiving insufficient pyridostigmine, transient improvement in symptoms will be seen;
  - *monitoring*: severe cholinergic reactions can result from the administration of edrophonium, particularly in the form of life-threatening bradycardia, arrhythmias, and hypotension. Cardiac telemetry is advised. Resuscitation facilities, particularly IV atropine (1–2mg) for urgent reversal of bradyarrythmia, should always be available for diagnostic procedures involving edrophonium.
- *Neostigmine*: should be commenced at a dose of 15mg every 3–4h and doubled every few days, according to response and side effects, up to a maximum of 75–300mg total daily dose. In severe disease, neostigmine can be given more frequently, usually in an inpatient setting.
  - *Monitoring*: clinicians should monitor for the development of muscarinic side effects such as colic, hypersalivation, and diarrhoea. These often limit the total daily dose patients can tolerate to around 180mg.
- *Pyridostigmine*: start treatment at 30mg tds, doubling every few days, according to response and side effects, up to a total daily dose of 1.2g (UK) or 1.5g (USA). A typical regimen is 60–90mg every 4–6h during the day.
  - *Monitoring*: clinicians prescribing pyridostigmine should monitor for the development of gastrointestinal muscarinic side effects.

Pharmacokinetics and interactions

Pharmacokinetics See Table A.2.

Interactions See Table A.3.

Table A.2 Pharmacokinetics of AChEIs

	Pyrido-stigmine	Neo-stigmine	Edro-phonium	Donepezil	Galanta-mine	Riva-stigmine
Indication	NMJ disorders			Dementia		
Admini-stration	PO, IV	IV, PO, SC	IV, IM	PO	PO	PO, TD
Onset of action	15min	1min	1–2min	NA	NA	NA
Duration of action	360min	20–30min	10min	NA	3h	NA
Oral bioavail-ability	10–20%	5%	NA	100%	88%	36%
T_{max} (h)	1–2	1–2	NA	3–4	1	1 (PO) 8–16 (TD)
Affected by food	Yes	Yes	NA	No	Yes	Yes
Protein binding	81%	15–25%	NA	95%	18%	40%
Cross BBB?	No	No	No	Yes	Yes	Yes
Metabolism	Negligible	Hepatic	Choline-sterases	CYP2D6/ 3A4	CYP2D6/ 3A4	Choline-sterases
Excretion	Urine 80%	Urine 50%	75% urine; 5% bile	Urine 57%	Urine 90%	Urine >90%
Elimination half-life	3–4h	77min	33–110min	70h	7h	1.5h

BBB, blood–brain barrier; IM, intramuscular; IV, intravenous; NA, information not available; PO, oral; TD, transdermal.

Table A.3 Interactions of AChEIs

Pharmacodynamic interactions
With aminoglycosides: effects of neostigmine and pyridostigmine antagonized.
With anticholinergics: diminished therapeutic effect.
With antipsychotics: enhanced neurotoxic effects, e.g. extrapyramidal symptoms (particularly donepezil and rivastigmine).
With β-blockers and other negative chronotropic agents: risk of arrhythmia and bradycardia.
With cholinergic agonists: enhanced toxicity.
With non-depolarizing neuromuscular blockers: AChEIs reduce neuromuscular-blocking effect.
With depolarizing neuromuscular blockers: AChEIs enhance neuromuscular-blocking effect.

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α2-adrenergic agonists

α2-adrenergic agonists are recognized as first-line agents for the treatment of moderate to severe tics, due to their relatively mild safety profile, when compared to antipsychotics. The latter, however, are regarded as the more effective agents by experts. The newer agent guanfacine is presumed to be better tolerated than clonidine; however, definitive comparative studies are lacking. They have been shown to be particularly effective in patients with co-morbid ADHD. Guanfacine is not widely available in European countries.

Uses

Off-licence uses

1. Clonidine: tics and TS.
2. Guanfacine: tics and TS.

Mechanism of action

Clonidine and guanfacine are centrally acting α2 receptor agonists. The α2-adrenoceptor is autoinhibitory and therefore inhibits the firing of noradrenergic neurons in the CNS. Clonidine has non-specific activity at α2A, B, and C receptors, as well as imidazoline receptors, while guanfacine preferentially binds α2A receptors. Their action in the locus caeruleus is thought to reduce sympathetic activity, resulting in their antihypertensive effect. Their beneficial effects in the management of tic disorder are less clear, although animal studies suggest that tic suppression and improved attention may be the result of improved connectivity of prefrontal cortical networks.

Toxicity and side effects

- *Common—cardiovascular*: bradycardia. *Dermatological*: application site reaction (transdermal clonidine). *Gastrointestinal*: anorexia, constipation, decreased appetite, dry mouth, elevated LFTs (alanine aminotransferase (ALT)), nausea, and vomiting. *Musculoskeletal*: weakness. *Neurological*: dizziness, drowsiness, fatigue, and headache.
- *Serious—cardiovascular*: arrhythmias, atrioventricular (AV) block, cardiac failure, MI, rebound hypertension, and tachycardia. *Dermatological*: exfoliative dermatitis. *Gastrointestinal*: colonic pseudo-obstruction. *Neurological*: convulsions and stroke. *Ophthalmological*: iritis. *Psychiatric*: hallucinations and mania.

Contraindications

- *Absolute*: known hypersensitivity to the drug or its constituents.
- *Relative*: bradycardia due to second- or third-degree AV block. Use with caution in patients with cardiovascular, cerebrovascular, or peripheral vascular disease and Raynaud's syndrome. Dose adjustment is advised in severe hepatic or renal impairment for both agents. Use the lowest effective dose, and assess for side effects which are more likely in patients with renal and liver disease (bradycardia, sedation, and hypotension).

Uses in special populations

- *Elderly*: no specific dose alterations are routinely required. Caution should be taken, as the elderly experience an age-related decline in renal and hepatic function and may be more prone to cardiovascular side effects.
- *Pregnancy*: limited data are available for the safety of these agents in pregnancy. Clonidine can cross the placenta and may lower fetal heart rate. The use of these agents in pregnancy should only be considered, if essential.
- *Lactation*: clonidine is present in breast milk; it is not known if guanfacine is too. The manufacturers advise avoidance in nursing mothers, as there are insufficient data as to whether these agents are harmful to infants.

Efficacy

A meta-analysis of six RCTs found α2-agonists to be beneficial in treating tic disorders in children (SMD = 0.31, 95% CI 0.15–0.48; p <0.001). However, subgroup analysis identified greatest efficacy in children with concomitant ADHD, and minimal benefit in those without ADHD. Significant publication bias is reported, based on funnel plot analysis. Correction for this still resulted in moderate, yet still significant, efficacy (SMD = 0.18, 95% CI 0.03–0.33). Comparative subgroup analysis showed no significant difference in efficacy between clonidine and guanfacine (p = 0.44). This may be the result of a relative lack of guanfacine trials.

Dosing and monitoring

1. *Clonidine*: start treatment at 25–50 micrograms/day, and increase every 2–3days by 25–50 micrograms/day. The normal maintenance dose is 100–300 micrograms/day.
2. *Guanfacine*: start treatment with the standard-release preparation at 0.5mg od at night for 3 days, then increase to 0.5mg bd for 4 days, and then to 0.5mg tds after a further week. This can be increased, as required, to 0.75–3mg/day in three divided doses.

Routine monitoring Consider ECG at baseline if risks factors or known cardiovascular disease. Treatment should be withdrawn gradually, due to the risk of rebound hypertensive crisis.

Pharmacokinetics and interactions

Pharmacokinetics See Table A.4.

Interactions See Table A.5.

Table A.4 Pharmacokinetics of α2-adrenergic agonists

	Clonidine	Guanfacine
Main routes of administration	PO/TD	PO
Bioavailability	70–80% (TD: 60%)	80–100%
T_{max}	1–3h	1–4h
Protein binding	30–40%	64%
Metabolism	Hepatic	Hepatic, mainly CYP3A4
Pharmacologically active metabolites	No	NA
Elimination half-life	12–16h	17h
Excretion	Urine, mainly as unchanged drug (70%), faeces (20%)	Urine ~50% as unchanged drug

NA, information not available; PO, oral; TD, transdermal.

Table A.5 Interactions of α2-adrenergic agonists

Medications which alter plasma levels	Pharmacodynamic interactions
Guanfacine (clonidine none): **levels decreased**: CYP3A4 inducers, e.g. carbamazepine, phenytoin, and St John's wort **levels increased**: CYP3A4 inhibitors, e.g. clarithromycin and fluoxetine	**With antihypertensives**: increased hypotensive effect **With β-blockers and TCAs**: risk of rebound hypertension on withdrawal—will need to be withdrawn slowly, if used together **With β-blockers, calcium channel blockers, cardiac glycosides**: may increase the risk of AV block **Clonidine (not guanfacine) with methylphenidate**: some reports have suggested an increased risk of death with this combination, although causality has not been established

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Anticholinergics

Anticholinergics act to inhibit the action of acetylcholine at nicotinic and muscarinic adrenergic receptors. Their main uses in neurology are as antimuscarinic agents in the treatment of PD tremor, other movement disorders (such as dystonia), and OAB associated with several neurological conditions such as MS. There are a large number of different antimuscarinics in clinical use which differ, depending on their muscarinic receptor selectivity and their ability to cross the blood–brain barrier. Only the drugs commonly used in the management of movement disorders and OAB syndrome are discussed further.

Anticholinergics were the first pharmacological agents used in the treatment of PD. In modern practice, they are usually used as adjuncts to levodopa, particularly in the treatment of tremor. Trihexyphenidyl is the most commonly used anticholinergic for treatment of PD in the UK, although clinically significant differences in efficacy and tolerability have not been established through clinical trials to help guide drug choice. The most commonly used agents benztropine, orphenadrine, procyclidine, and trihexyphenidyl have less peripheral effects than other antimuscarinics, but CNS side effects, both neuropsychiatric and cognitive, can limit their use in the elderly.

An increasing number of antimuscarinics are used in the management of OAB; the commonest antimuscarinics in use for this indication are oxybutynin, solifenacin, and tolterodine, and are mentioned in further detail in later text and compared further in Chapter 17, Uro-neurology. These are first-line medical agents for OAB. They can significantly improve a patient's quality of life and are generally safe and well tolerated. Side effects are often predictable and dose-dependent.

Uses

Licensed uses

In the UK

- *Parkinsonism*:
  1. *benztropine* is not available in the UK;
  2. *orphenadrine* is licensed for the treatment of all forms of parkinsonism, including drug-induced extrapyramidal side effects in individuals aged 18 years and older;
  3. *procyclidine* is licensed for use in the management of all forms of parkinsonism in individuals aged 18 years and older.

In the USA

- *Parkinsonism*:
  1. *benztropine* is licensed for use as an adjunct in the treatment of all forms of parkinsonism in individuals aged 18 years and older.
- *Drug-induced extrapyramidal disorder*:
  1. *benztropine* is used for the control of acute and chronic extrapyramidal symptoms in individuals aged 18 and older.
- *Muscle spasm*:
  1. *orphenadrine* is licensed for the treatment of painful musculoskeletal conditions, as an adjunct to rest and physical therapy, in individuals aged 18 years and older.

In the UK/USA

- *Parkinsonism and drug-induced extrapyramidal disorder*:
  1. *procyclidine* is licensed for the management of extrapyramidal symptoms induced by neuroleptic drugs in individuals aged 18 years and older;
  2. *trihexyphenidyl* is licensed in the treatment of extrapyramidal disorders due to neuroleptic drugs in individuals aged 18 years and older.

Off-licence uses

- Dystonia (generalized or as an adjunct to botulinum toxin in focal forms), ET, and Holmes' tremor.
- DRD.

Mechanism of action

- *PD*: with the loss of inhibitory dopaminergic drive in PD, there is excess excitatory cholinergic activity within the striatum. Anticholinergics in PD and other extrapyramidal movement disorders are thought to rebalance the cholinergic and dopaminergic activity of the striatum, thereby improving extrapyramidal symptoms.
- *OAB*: muscarinic antagonists act through inhibition of types 2 and 3 muscarinic receptors to relax detrusor muscle.

Toxicity and side effects

- *Common—cardiovascular*: hypotension and tachycardia. *Gastrointestinal*: constipation, decreased gastric motility, dry mouth, nausea, and vomiting. *Dermatological*: rash. *Endocrine*: decreased sweating. *Neurological*: dizziness and memory impairment. *Ophthalmological*: blurred vision, diplopia, dry eyes, and mydriasis. *Psychiatric*: agitation, confusion, euphoria, and hallucinations. *Respiratory*: reduced bronchial secretions. *Urological*: prostatism and urinary retention.
- *Serious—cardiovascular*: angina. *Ophthalmological*: angle-closure glaucoma.

Contraindications

- *Absolute*: hypersensitivity to drug and closed-angle glaucoma.
- *Relative*: gastrointestinal obstruction, prostatism, tachycardia, and cognitive impairment. May exacerbate tardive dyskinesia and MG. As anticholinergics are metabolized by the liver and excreted in the urine, caution is advised in liver and renal impairment; however, no dose alteration is routinely recommended.

Uses in special populations

- *Elderly*: the elderly are more susceptible to cognitive and psychiatric side effects of anticholinergics, which may preclude their use in this group of patients.
- *Pregnancy*: safety in pregnancy has not been studied. There are case reports of the safe use of trihexyphenidyl in pregnancy, but there has been reproductive toxicity in animal studies of antimuscarinics used for OAB; hence the manufacturer advises against use in pregnancy, where possible.
- *Lactation*: excretion into breast milk is not known for most anticholinergics. Use with caution.

Efficacy

- *OAB*: meta-analyses have demonstrated there are no major differences in efficacy between the different agents, and they share a similar side effect profile, which includes effects such as dry mouth and cognitive impairment. Individual variations relate to their muscarinic receptor selectivity, pharmacokinetics, and metabolism. Eighty-five per cent of patients who have failed dosage-escalated monotherapy were shown to benefit from combined high-dosage antimuscarinic medications. Combination ISC and antimuscarinic agents may provide greatest benefit.

  A Cochrane systematic review of anticholinergics for the treatment of MS-related urinary symptoms identified 33 articles, of which three were of sufficient quality to be appraised. Based on these trials, they conclude that anticholinergic use could not be advocated for the treatment of MS-related urinary symptoms. However, this conclusion is likely the result of a lack of high-quality research in this area, and these agents remain commonly used in MS. A high rate of adverse events was noted by the review, with one in five trial patients withdrawing because of them.
- *PD*: a Cochrane review of anticholinergic drug treatments, including benzhexol/benztropine and orphenadrine, in PD was published in 2009. Eight of the nine studies included showed significant improvements in motor symptoms from baseline. The largest cause of patient withdrawal from trials was neuropsychiatric side effects. The MDS evidence-based review concluded anticholinergics were 'likely efficacious' as symptomatic monotherapy and as an adjunct to levodopa. In the UK, NICE guidelines suggest anticholinergics should only be used as monotherapy in young-onset PD or in patients with severe tremor, and should not be the first choice outside of these cases due to a lack of evidence for their efficacy and a propensity for neuropsychiatric side effects.

Trihexyphenidyl (benzhexol)

- *Dystonia*: trihexyphenidyl is the only anticholinergic assessed in a double-blind trial (n = 31, 32 years or younger) for the treatment of dystonia (torsion dystonia). Seventy per cent had a clinically significant response, with sustained benefit noted in 42% after a mean follow-up of 2.4 years.
- *Parkinsonism*: there are minimal robust efficacy data for the use of trihexyphenidyl in PD. A 6-month randomized, double-blind study (n = 30) with either levodopa alone or in combination with trihexyphenidyl concluded there was no additional benefit to combination treatment. However, methodological flaws in trial design cast doubt on the validity of this result.

Benztropine

- *Parkinsonism*: there is limited evidence from small trials suggesting benztropine is effective in the management of PD. One randomized, double-blind, placebo-controlled, cross-over study (n = 29) found benztropine used as an adjunct in patients on levodopa significantly improved activities of daily living, rigidity, speed of walking, and movement of upper extremities. A further non-randomized,

double-blind, cross-over trial (n = 22) comparing benztropine (mean dose 3g/day) and clozapine for tremor in PD found both agents to be equally effective, with a 30% reduction in tremor.

Orphenadrine

- *Parkinsonism*: a randomized, double-blind, cross-over study of orphenadrine (titrated to 300mg/day) vs placebo (n = 16) found significant benefits in balance, posture, walking, rigidity, household tasks, and total physical signs and disabilities (p <0.05). These were rated on the author's own 4-point scale. No significant improvement in tremor was noted.

Procyclidine

- *Parkinsonism*: there are minimal robust trial data for the efficacy of procyclidine in parkinsonism. A 2-month non-randomized trial that investigated the use of procyclidine as an adjunct to other antiparkinsonian medication in patients with parkinsonism (n = 70) showed improvement in tremor (40%), rigidity (53%), akinesia (42%), gait (44%), and sialorrhoea (58%).

Dosing and monitoring

Trihexyphenidyl (benzhexol)

- *Parkinsonism*: start treatment at 1mg, and increase every 4–7 days by 2mg until maximal symptomatic relief and tolerability. The total daily dose can be divided over the day (tds to qds) and should be given before or after meals. In PD, a dose of 6–10mg/day is usually adequate. Post-encephalitic parkinsonism may require up to 15mg/day. Up to half of patients may initially experience minor side effects that will resolve, as they develop tolerance, although, in some cases, this will preclude continued use or dose escalation.
- *Dystonia and ET*: start at 1mg daily, and increase by 1mg every 4–7 days to reach 1mg tds. Then increase by 1mg every 4–7 days to reach a usual maintenance dose of 2–4mg tds. Stop dose escalation if side effects occur, and consider restarting after 1–2 weeks.

Benztropine

- *Parkinsonism*: start treatment at 0.5mg/day. Increase every 5–6 days by 0.5mg to achieve maximal symptomatic relief. This can be given once at night or in 2–4 divided doses throughout the day. The usual maintenance dose is 1–2mg/day. Maximum daily dose is 6mg. Higher doses are often required for drug-induced extrapyramidal disorders.
- *Acute dystonic reactions*: 1–2mg IV/IM every 8–12h. Switch to PO after management of acute reaction, and withdraw after 1–2 weeks to assess the need for continued therapy.

Orphenadrine

- *Parkinsonism*: start treatment at 150mg daily in divided doses. Increase gradually in steps of 50mg every 2–3 days, according to response. The usual maintenance dose range is 150–300mg daily in divided doses. The maximum dose is 400mg/day.

Procyclidine

- *Parkinsonism*: 2.5mg tds, increased gradually in steps of 2.5–5mg daily every 2–3 days, if necessary. Maximum 30mg/day in 2–4 divided doses (60mg daily in exceptional circumstances).
- *Acute dystonic reactions*: 5–10mg IM/IV, usually effective in 5–10min but may need 30min for relief.

Routine monitoring No routine monitoring is required.

Drugs used in the management of OAB.

Pharmacokinetics and interactions

Pharmacokinetics See Table A.6.

Interactions See Table A.7.

Table A.6 Pharmacokinetics of anticholinergics

	Benztropine	Orphenadrine	Procyclidine	Trihexyphenidyl	Oxybutynin	Solifenacin	Tolterodine
Indication	Extrapyramidal disorders				OAB		
Main routes of administration	PO/IV/IM	PO/IV/IM	PO IM/IV	PO	PO	PO	PO
Oral bioavailability	NA	90%	75%	100%	10%	90%	77%
T_{max}	7h	2h	1h	2–3h	1h	1–2h	1–3h
Protein binding	NA	95%	100%	NA	93%	98%	96%
Metabolism	Hepatic	Hepatic	Hepatic	NA	Hepatic	Hepatic	Hepatic
Elimination half-life	NA	13–20h	12h	NA	2–5h	45–68h	2–4h
Elimination routes	Urine	Urine and bile	Urine	Urine	Urine	Urine and faeces	Urine and faeces

IM, intramuscular; IV, intravenous; NA, information not available; PO, oral.

Table A.7 Interactions of anticholinergics

Pharmacodynamic interactions
With AChEIs, e.g. donepezil, galantamine, and rivastigmine: may reduce the anticholinergic effects
With other anticholinergics: may increase risk of anticholinergic side effects
With sublingual tablets, e.g. nitrates: may reduce absorption due to failure to dissolve in dry mouth
With drugs that prolong QT interval, e.g. erythromycin: may prolong QT interval

Antihistamines

The antihistamines are a large group of drugs commonly used in the management of vertigo and nausea associated with vestibular disorders. The agents most commonly used for vertigo in the UK are cinnarizine and cyclizine. In the USA, cyclizine, diphenhydramine, and meclizine are favoured. Diphenhydramine is often used in combination with a weak theophylline to form dimenhydrinate. Theophylline is a weak stimulant and is used to counteract sedative side effects.

All of these drugs are antagonists at the H1 receptor, the majority also having strong anticholinergic activity which probably contributes to their therapeutic activity, as well as their side effect profile. Their main differences arise from their pharmacological structure and pharmacokinetic profiles (see further text). Betahistine is a histamine-like agent commonly used in the management of Ménière's disease in Europe. Its dominant actions are H1 receptor agonism and H3 receptor antagonism; hence it is discussed separately in its own monograph (see Betahistine, pp. 408–9).

The dominant side effect of these agents is sedation, and patients should be warned of this and advised to avoid the use of heavy machinery while on treatment. Unlike the newer second-generation antihistamines, the older agents used in the treatment of vertigo cross the blood–brain barrier and interact with histaminergic pathways involved in sleep and alertness, so causing sedation. This central action is thought to be important for antivertigo efficacy, as the beneficial effects are not routinely seen in the newer less sedating agents. Use is typically restricted to 24–48h, depending on the extent and duration of symptoms, as there are concerns that the vestibular suppressive effect of these medications may prevent the natural process of vestibular compensation, thereby prolonging symptoms.

Uses

Licensed uses

In the UK

- *Vertigo*:
  1. *cinnarizine* is licensed for the treatment of vestibular disorders, including vertigo, tinnitus, nausea, and vomiting, in individuals aged 5 years and older;
  2. *cyclizine* is licensed for the treatment of vomiting and attacks of vertigo in disorders of vestibular disturbance in individuals aged 6 years and older;
  3. *dimenhydrinate* is not licensed for use in the UK;
  4. *diphenhydramine* is not licensed for the treatment of vertigo in the UK;
  5. *meclizine* is not licensed for use in the UK.

In the USA

- *Vertigo*:
  1. *cinnarizine* is not licensed for use in the USA;
  2. *cyclizine* is licensed for the treatment of vertigo associated with motion sickness in individuals aged 6 years and older;

3. *dimenhydrinate* is licensed for the treatment of nausea, vomiting, and vertigo associated with motion sickness in individuals aged 2 years and older;
4. *diphenhydramine* is licensed for nausea, vomiting, and vertigo associated with motion sickness in individuals aged over 1 month;
5. *meclizine* is licensed for the treatment of vertigo associated with diseases affecting the vestibular system in individuals aged 12 years and older.

Off-licence uses

- Migraine-associated vertigo and vertigo of vestibular origin.

Mechanism of action

Cinnarizine, cyclizine, diphenhydramine, and meclizine are all H1 receptor antagonists and are believed to reduce the symptoms of vertigo by blocking the effects of histamine on smooth muscle in the hair cells of the vestibular canal, thereby rendering the organs less sensitive. Some of their beneficial effects may also be mediated by central anticholinergic and antihistaminergic activity. Cinnarizine may additionally act as an L-type calcium channel blocker and a pressure-sensitive potassium channel blocker, thereby inhibiting the release of neurotransmitters at synaptic terminals supplying the vestibular organs and minimizing vertigo.

Toxicity and side effects

- *Common—gastrointestinal*: dry mouth, dyspepsia, and nausea. *Neurological*: drowsiness and headache. *Ophthalmological*: blurred vision.
- *Serious—cardiovascular*: arrhythmias, hypotension, and QT prolongation. *Gastrointestinal*: hepatic dysfunction. *Haematological*: agranulocytosis. *Immunological*: anaphylaxis, angio-oedema, bronchospasm, and lupus-like skin reactions. *Neurological*: convulsions and extrapyramidal effects, including psychomotor impairment. *Ophthalmological*: angle-closure glaucoma.

Contraindications

- *Absolute*: hypersensitivity to the individual antihistamine or its excipients. All antihistamines mentioned in this section should be avoided in porphyria.
- *Relative*: use with caution in patients susceptible to angle-closure glaucoma and in patients who suffer from epilepsy, obstructive disease of the gastrointestinal tract, parkinsonism, prostatic hypertrophy, or urinary retention.

No specific studies have been performed in patients with hepatic and renal dysfunction; hence antihistamines should be used with caution in these groups and avoided in patients with moderate to severe hepatic impairment, as they may precipitate coma.

Uses in special populations

- *Elderly*: dosing is typically the same as adult doses; however, the elderly are more prone to sedative and anticholinergic side effects.
- *Pregnancy*: animal studies have not shown teratogenicity. However, there have been no controlled studies in humans; hence as a precaution, manufacturers advise avoidance of antihistamines in pregnancy, where possible.
- *Lactation*: for many of the antihistamines, it is not known whether they are excreted into breast milk; hence, as a precaution, the manufacturers advise avoidance, where possible, by nursing mothers.

Efficacy

Evidence for efficacy of most antihistamines comes from small early studies demonstrating good effect in reducing the severity and frequency of vertigo attacks. Rationale for use is based on these studies and expert consensus. There is no conclusive evidence that any one antihistamine is more effective than another in the management of vertigo. There is some evidence that combining two antihistamines, specifically dimenhydrinate and cinnarizine, may be more effective than either agent alone; one RCT investigating acute unilateral vestibular loss found that combination treatment with 20mg cinnarizine and 40mg dimenhydrinate was significantly more effective than either agent alone (p <0.001) after 1 and 4 weeks of treatment. Within the context of Ménière's disease, one small, non-randomized trial of 37 patients concluded that betahistine was more effective than cinnarizine for the relief of vertigo at 4 weeks. Further larger and better-quality studies are needed to corroborate these findings.

Dosing and monitoring

- *Cinnarizine*: 30mg up to tds.
- *Cyclizine*: 50mg up to tds.
- *Diphenhydramine*: 25–50mg every 6h. Up to 100mg can be given qds, if required.
- *Dimenhydrinate*: 50–100mg up to qds. Maximum daily dose is 400mg.
- *Meclizine*: treatment is 25–100mg/day in divided doses.

Routine monitoring None is required.

Pharmacokinetics and interactions

Pharmacokinetics See Table A.8.

Interactions See Table A.9.

Table A.8 Pharmacokinetics of antihistamines

	Cinnarizine	Cyclizine	Diphenhydramine	Meclizine
Main routes of administration	PO	IV/IM/PO/SC	PO/IM/IV	PO
Oral bioavailability	Highly variable	~50%	40–60%	NA
T_{max}	2.5–4h	2h	2h	3h
Protein binding	91%	NA	98.5%	91–99%
Metabolism	Hepatic: CYP2D6	Hepatic: demethylation	Hepatic: CYP2D6	Hepatic: CYP2D6
Elimination half-life	3–6h	~14h	9h	5–6h
Elimination	1/3 urine; 2/3 stool	Urine as metabolites	Urine as metabolites	Urine and faeces—exact proportion not known

NA, information not available.

Table A.9 Interactions of antihistamines

Pharmacodynamic interactions
With alcohol and other CNS depressants: increased risk of sedation
With betahistine and histamine: antagonism (theoretical in the case of betahistine) of effects of these drugs
With monoamine oxidase inhibitors (MAOIs) and TCAs: increased risk of anticholinergic and sedative side effects

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Atypical antipsychotics

The atypical antipsychotics (risperidone, olanzapine, quetiapine, clozapine, and aripiprazole) are associated with a reduced rate of tardive dyskinesia, compared with their typical predecessors. For this reason, they are now favoured for the treatment of several neurological conditions. Risperidone, olanzapine, and aripiprazole has largely replaced the use of haloperidol and pimozide in the management of tic disorders; quetiapine and clozapine are widely used in the treatment of PD psychosis and olanzapine; risperidone and sulpiride can be used second-line in the management of chorea. Although having an improved neurological side effect profile, atypical antipsychotics carry a significant risk of metabolic syndrome, as characterized by obesity, insulin resistance, hypertension, and dyslipidaemia, parameters which require regular monitoring and management. Clozapine, although a very effective drug for PD psychosis, is associated with agranulocytosis, which requires registration to a clozapine monitoring service and regular monitoring of FBC.

Uses

Licensed uses

In the UK

- *PD*.
  1. *Clozapine* is licensed for the treatment of psychotic disorders arising in PD where standard therapies have failed in individuals aged 18 years and older.

Off-licence uses

1. *Aripiprazole*: tics and TS.
2. *Clozapine*: chorea and dystonia.
3. *Risperidone*: chorea, tics, and TS.
4. *Quetiapine*: psychosis present in PD and DLB.

Mechanism of action

Their action is primarily through inhibition of dopaminergic receptors. Compared to typical antipsychotics, they are associated with a reduced incidence of extrapyramidal side effects, which may be the result of their additional affinity for serotonergic receptors. The wider receptor profiles of each agent are highlighted in Table A.10 and can be used to predict likely side effects.

Table A.10 Relative receptor affinities of atypical antipsychotics

Drug	D1	D2	D3	D4	5HT1	5HT2	5HT2A	α1	α2	ACh	H1
Aripiprazole	+	++++	?	?	++	?	+++	–	-	++	-
Clozapine	+	++	?	+	+	++	+	+++	+++	+++	++
Olanzapine	++	+++	+	+	–	++	++	+++	+	+	+++
Risperidone	+	+++	?	+	+	–	+++	+++	+++	-	+
Quetiapine	+	++	+	–	–	+	+++	+++	+	-	+++

++++, very high; +++, high; ++, moderate; +, low; ?, unknown.

Adapted from *CNS Spectrums*, 10(S10), Fernando Cañas, Mechanisms of Action of Atypical Antipsychotics, pp. 5–11, Copyright (2005), with permission from Cambridge University Press.

Toxicity and side effects

- *Common—cardiovascular*: peripheral oedema and tachycardia. *Gastrointestinal*: abdominal pain, appetite increased, constipation, drooling, elevated liver enzymes, nausea, vomiting, and weight gain. *Neurological*: akathisia, anxiety, dizziness, fatigue, headache, insomnia, sedation, and somnolence.
- *Serious—cardiovascular*: arrhythmia, AV block, cardiac arrest, chest pain, and ischaemic heart disease. *Gastrointestinal*: aspiration, hepatic failure, hypercholesterolaemia, intestinal obstruction, and pancreatitis; *haematological*: agranulocytosis and thrombotic thrombocytopenic purpura. *Neurological*: akinesia, NMS, seizures, stroke, and tardive dyskinesia. *Ophthalmological*: angle-closure glaucoma. *Psychiatric*: depression, homicidal ideation, intentional injury.

In addition, with clozapine:

- *serious—cardiovascular*: cardiomyopathy, myocarditis, and QT prolongation. *Haematological*: agranulocytosis (rare—0.38% in one cohort, not dose-dependent).

Contraindications

- *Absolute*: hypersensitivity to drug or its excipients.
- *Relative*: use with caution in patients with epilepsy, predisposition to long QT syndrome, cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension.
  1. *Aripiprazole*: pathological gambling has also been associated with aripiprazole use, so use with caution in patients with a prior history of gambling. No dosage adjustment in renal or mild to moderate hepatic impairment. Use with caution in severe impairment.
  2. *Clozapine*: due to anticholinergic effects, caution should be taken with those with prostatic hypertrophy and susceptibility to angle-closure glaucoma. No dosage adjustment in mild to moderate renal impairment or mild hepatic impairment.
  3. *Risperidone*: patients with impaired hepatic or renal function should have their doses halved, and uptitration should occur cautiously with minimal increments in doses.
  4. *Quetiapine*: no dose alteration in renal dysfunction. In hepatic impairment, start at a lower dose, due to extensive liver metabolism. Immediate-release: 25mg daily; increase dose by 25–50mg daily to effective dose. Extended-release: 50mg od; increase dose by 50mg/day, as tolerated.

Uses in special populations

- *Elderly*: no dosage alteration is routinely recommended; however, the elderly are more prone to orthostatic hypotension, and trials of antipsychotics in elderly patients with dementia have suggested that there is an increased incidence of cerebrovascular events.
- *Pregnancy*: adverse events have been noted in animal studies; however, teratogenicity has not been identified so far in limited human data. Neonates born to mothers taking antipsychotics may exhibit

extrapyramidal signs or withdrawal signs. Atypical antipsychotics should only be used in pregnancy if the benefits outweigh the risks.
- *Lactation*: all of the atypical antipsychotics mentioned are excreted in breast milk; the manufacturers recommend avoidance by nursing mothers.

Efficacy

1. *Aripiprazole*: a 10-week multicentre, double-blind, randomized, placebo-controlled trial ($n = 61$) of aripiprazole in children and adolescents with TS found that there was a significant reduction in Yale Global Tic Severity Scale (YGTSS), compared to placebo (−15.0 vs −9.6, respectively; $p = 0.0196$). A further RCT ($n = 60$) comparing aripiprazole with risperidone over 2 months of treatment suggested there was little difference in improvement of YGTSS and health-related quality of life scores between medications, although risperidone was found to improve patient social functioning more than aripiprazole.
2. *Clozapine*: has been shown in several double-blind RCTs to be effective in the treatment of PD psychosis. The first study to demonstrate its effectiveness reported that the Clinical Global Impression score (a score of symptom severity in disorders of mental health) improved by 1.8, compared to 0.6 in the placebo group ($p = 0.001$). It was well tolerated at 6.25–50mg/day (doses used in schizophrenia being far higher at 300–800mg/day). Both this study and a further European RCT have suggested that the symptoms of parkinsonism were not worsened at these doses; in fact, tremor may improve with treatment. The recent MDS review classed it as efficacious and that the associated risks are acceptable so long as treatment is carefully monitored.
3. *Risperidone*: is the best studied atypical antipsychotic for treatment of tics and TS. Efficacy vs placebo has been demonstrated in two RCTs of both children and adults with mean daily doses of about 2.5mg (range 1–6mg/day). In two randomized, double-blind, cross-over studies, it was at least equally effective and possibly slightly more effective than pimozide. Risperidone may also be beneficial for coexistent aggressive behaviour and obsessive–compulsive symptoms. A survey of expert opinion, published within the European guidelines for treatment of TS, highlights risperidone as the first-line treatment of choice for tics in children and adolescents. However, due to the wider side effect profile of antipsychotics, $\alpha 2$-adrenergic agonists are often used first-line in patients with moderate-severity tics.
4. *Quetiapine*: has been studied in several trials (open-label and double-blind, placebo-controlled trials) with conflicting results. Open-label studies showed it to be ineffective but well tolerated, without motor worsening. Small, low-quality double-blind trials have suggested it may be effective. Expert consensus suggests it is useful in treating PD psychosis when used at low doses; it only carries limited risk of motor worsening, and its side effect profile is significantly better than clozapine, and hence it is often used first-line for this indication.

Dosing and monitoring

1. *Aripiprazole*: start treatment at 2.5mg; this can be increased by 1.25–2.5mg in 1-week intervals, as required/tolerated, to a maximum daily dose of 30mg. The largest case series to date (n = 100) found great variation in maintenance dose, with mean doses of 17.0 ± 9.6mg.
2. *Clozapine*: start treatment at 6.25–12.5mg at night, and increase by 12.5mg no more than twice a week. The minimal effective dose is usually 25–37.5mg/day. The maximum recommended dose is 50mg/day, although rarely doses of 100mg/day in 1–2 divided doses have been used. Once maintenance dose is reached, this should be maintained for 2 weeks before PD medications are altered.
   - *Clozapine monitoring*: all patients should be registered with a clozapine monitoring service. An FBC should be taken at baseline, then weekly for 18 weeks, and monthly thereafter, in view of the risk of agranulocytosis. Stop the drug if absolute neutrophil count is $<1.5 \times 10^9$/L or WCC $<3.0 \times 10^9$/L.

   Patients should be advised that, if they experience flu-like symptoms, a rash, or a fever, which may indicate a low WCC or agranulocytosis, they should stop the drug and seek urgent medical advice.

   If stopping for a reason other than a serious or life-threatening side effect, the dose should be tapered over 1–2 weeks, with 12.5mg interval reductions. Monitor for rebound psychosis.
3. *Risperidone*: start treatment at 0.25mg od for 2 days, then increase to 0.5mg/day in two divided doses for 3 days, then 1g/day in two divided doses for 3 days. Thereafter, increase in increments of 0.5mg/day every 3–4 days, as required/tolerated, up to a usual maintenance dose of 2.5mg/day. The maximum dose used in trials was 6mg/day.
4. *Quetiapine*: start treatment at 12.5–25mg at night. Increase every 1–2 days, until symptoms improve. The usual effective dose is 75–200mg in 2–3 divided doses. The maximum dose is 200mg/day.

Routine monitoring Monitor body mass index (BMI), BP, FBC, glucose, and thyroid, renal, and liver function, as well as lipid panels, on a regular basis.

Pharmacokinetics and interactions

Pharmacokinetics See Table A.11.

Interactions See Table A.12.

Table A.11 Pharmacokinetics of atypical antipsychotics

	Aripiprazole	Clozapine	Quetiapine	Risperidone
Main routes of administration	PO	PO	PO	PO
Oral bioavailability	87%	60–70%	9%	70%
T_{max}	1–3h	2.5h	1.5h	1h
Protein binding	99%	95%	83%	90%
Metabolism	Hepatic CYP2D6, CYP3A4	Hepatic CYP1A2, CYP3A4	Hepatic CYP3A4	Hepatic CYP2D6, CYP3A4
Pharmacologically active metabolites	Yes, dehydro-aripiprazole	Yes, norclozapine	Yes, *N*-desalkyl-quetiapine	Yes, 9-hydroxy-risperidone
Elimination half-life	75h	8–12h	3h	3h
Excretion	Urine (27%), faeces (60%)	Urine (50%), faeces (30%)	Urine (73%), faeces (21%)	Urine (70%), faeces (14%)

PO, oral.

Table A.12 Interactions of atypical antipsychotics

Medications which alter atypical antipsychotic plasma levels	Pharmacodynamic interactions
Levels increased: CYP3A4, CYP2D6, and CYP1A2 inhibitors **Levels decreased**: CYP3A4, CYP2D6, and CYP1A2 inducers (dependent on method of metabolism; see pharmacokinetics, Table A.11)	**With CNS depressants, e.g. alcohol**: enhanced sedative effects **With agents known to prolong QTc, e.g. chlorpromazine and macrolide antibiotics**: increased risk of ventricular arrythmia **With other antipsychotics (e.g. sulpiride)**: may increase the risk of antipsychotic toxicity **With tetrabenazine**: increased risk of extrapyramidal side effects

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Benzodiazepines

Chlordiazepoxide was the first benzodiazepine to be synthesized in 1955, shortly followed by diazepam in 1963. Benzodiazepines are used for a wide range of indications within neurology, including epilepsy, insomnia and other sleep disorders, spasticity, and movement disorders. While being highly effective for the majority of these indications, the drawbacks of all benzodiazepines are that they carry the risk of rebound seizures if withdrawn too rapidly, sedative side effects are common, and they are all potential drugs of abuse.

Within the context of epilepsy, there are two main groups of benzodiazepines. The first group, comprising diazepam, lorazepam, and midazolam, is primarily used in the early management of status epilepticus. They are highly effective, and have a rapid onset of action and multiple routes of administration. The second group includes clobazam and clonazepam, drugs more commonly used in the longer-term management of chronic epilepsy, typically as an adjunct when first- and second-line treatments have failed. They are useful against a wide range of seizure types and can result in dramatic seizure reduction in apparently refractory cases, or, in the case of clobazam, when used short-term, to manage acute flares of seizure activity. However, a large proportion of patients will develop tolerance if used in the medium to long term. Temazepam is the final benzodiazepine to be discussed in this book; unlike the aforementioned drugs, it has not found a use in epilepsy, but rather it is used for its sedative effects in the short-term management of insomnia.

Uses

Licensed uses

In the UK

- *Epilepsy*:
  1. *clobazam* is licensed for the treatment of non-convulsive status epilepticus and as intermittent adjunctive therapy in the treatment of partial or generalized seizures in individuals over 3 years old;
  2. *clonazepam* is licensed for the treatment of generalized seizures, including absence, clonic, myoclonic, tonic, and tonic–clonic types. It is also licensed in the treatment of focal-onset seizures with or without secondary generalization. As an IV infusion, it is licensed in the treatment of status epilepticus. All of its licences are for individuals of all ages;
  3. *diazepam*: the oral/rectal form is licensed for the treatment of epileptic and febrile convulsions. The oral form is licensed as an adjunct in certain types of epilepsy, e.g. myoclonus. The IV form is licensed in the treatment of status epilepticus and febrile convulsions;
  4. *lorazepam* is licensed for the treatment of status epilepticus in its IV form in individuals of all ages;
  5. *midazolam*: the oromucosal form is licensed for the treatment of prolonged, acute, convulsive seizures in individuals aged from 3 months to <18 years of age.

In the USA

- *Epilepsy*:
  1. *clobazam* is licensed for adjunctive therapy of LGS in patients 2 years or older;
  2. *clonazepam* is licensed for the treatment of akinetic, absence, and myoclonic seizures, as well as LGS, in individuals of all ages;
  3. *diazepam*: the rectal form is licensed for the treatment of refractory epilepsy as an intermittent therapy to control bouts of increased seizure frequency. The oral form is licensed for use as an adjunct in the treatment of convulsive disorders. The IV form is licensed for use in status epilepticus;
  4. *lorazepam* is licensed for the treatment of status epilepticus in its IV form in individuals of all ages;
  5. *midazolam* is not licensed for the treatment of epilepsy in the USA.

Off-licence uses

1. *Clobazam* is used in the management of catamenial epilepsy and withdrawal epilepsy.
2. *Clonazepam* is used in the management of ET, myoclonus (both cortical and subcortical), nocturnal spasm, parasomnias (non-REM and RBD), RLS, short-term relief of spasticity, and tic disorders.
3. *Lorazepam* is used in the management of myoclonic seizures.
4. *Midazolam* can be used as intermittent therapy to control acute repetitive seizures and for the control of status epilepticus in adults.

Mechanism of action

The benzodiazepines share certain pharmacological properties. As a group, they bind to ionotropic GABA-A ligand-gated chloride channel complexes, potentiating the action of GABA by increasing transmembrane chloride conductance. The resulting post-synaptic hyperpolarization inhibits the propagation of action potentials.

Certain benzodiazepine agents are used preferentially in epilepsy, and others as anxiolytics or hypnotics, for two reasons:

1. differences in pharmacokinetic profile (determined, in large part, by the varying degree to which a benzodiazepine is lipid-soluble);
2. individual benzodiazepines have varying activity at different GABA-A receptor subunits; GABA-A channels are synthesized from a number of different subunits, which are uniquely distributed throughout the nervous system. Individual subunits have different clinical impacts. For example, the α-1-GABA-A subunit mediates anticonvulsant activity and some sedative side effects of benzodiazepine treatment, while the α-2-GABA-A subunit is important in anxiolysis.

Toxicity and side effects

- *Common—gastrointestinal*: anorexia, constipation, and dry mouth. *Neurological*: fatigue and drowsiness are common and can sometimes be severe—this is often minimized by smaller doses and giving the medication at night, and confusion and ataxia can occur, particularly in the elderly. *Psychiatric*: behavioural disturbances are also relatively

common—aggression, depression, insomnia, and hyperactivity can occur, particularly in the elderly.
- *Serious—cardiovascular*: acute IV administration may result in hypotension. *Haematological*: blood dyscrasias have rarely been reported. *Neurological*: withdrawal syndrome following chronic use, including rebound seizures, if suddenly stopped. *Psychiatric*: dependence, tolerance, and withdrawal phenomena. *Respiratory*: rarely respiratory depression and apnoea can occur.

Contraindications
- *Absolute*: individuals with a risk of respiratory depression, including: acute pulmonary disease, obstructive sleep apnoea, marked respiratory muscle weakness, and pre-existing respiratory depression. They are also contraindicated in severe hepatic impairment.
- *Relative*: pre-existing mood disorders, e.g. chronic psychosis, depression, and obsessional/phobic disorders. A history of drug or alcohol abuse and in those with muscular weakness, including MG. Smaller doses are recommended in patients with renal impairment, as benzodiazepines are renally excreted, and these individuals tend to be more sensitive to side effects. Reduce the dose in mild to moderate hepatic impairment.

Uses in special populations
- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function and benefit from lower dosing regimens. Co-prescription of other medications is also more likely in the elderly, and hence the risk of pharmacokinetic interactions is high.
- *Pregnancy*: human studies have demonstrated teratogenic potential for many of the benzodiazepines. Neonates are at risk of flaccidity and withdrawal. Use in pregnancy involves weighing up the potential benefits and side effects (see Antiepileptic drugs in young women, pp. 37–9).
- *Lactation*: all of the benzodiazepines are present, to varying extent, in mammalian breast milk. If used by nursing mothers, infants should be monitored for potential side effects such as drowsiness and poor interaction. They should be switched to alternative methods of feeding if these are identified.

Efficacy
1. *Clobazam*: several RCTs have shown a 50% or greater reduction in seizure frequency, compared to placebo, in 52–57% of patients treated for refractory partial epilepsy. A 2008 Cochrane review concluded that it may have most benefit in focal-onset seizures. Thirty per cent of patients treated with clobazam never develop tolerance. One large Canadian retrospective study found that, in up to 50% of patients, clobazam can be used for 4 years or more prior to the development of clinically significant tolerance.
2. *Clonazepam*: evidence for the use of clonazepam for any of its indications are typically based on observational studies, and there is little concrete evidence of efficacy in the form of RCTs. Many case series and trials have noted high levels of dropout due to side effects, predominantly ataxia, confusion, and sedation.

- *Epilepsy*: clonazepam is thought to be particularly effective in the management of myoclonic seizures.
- *ET*: evidence is conflicting, with some studies suggesting no effect and others minimal improvement in tremor.
- *Myoclonus*: strong conclusions cannot be drawn from studies; however, expert opinion suggests clonazepam is probably effective.
- *Parasomnias*: the best practice guide for management of RBD (2010) identified from 22 studies (predominantly case series) that 306 out of 339 patients had a complete or partial response to treatment. There is less evidence for use in non-REM parasomnias, although some case series of patients with injurious sleepwalking and sleep terrors showed that patients could have a sustained response to clonazepam over a mean period of 3.5 years.
- *RLS*: clonazepam improves sleep quality but does not have an effect on the core clinical symptoms of RLS. One small RCT ($n = 6$) found significant improvement in RLS-related sleep efficiency (89% vs 73% with placebo) with 1mg of clonazepam.
- *Spasticity*: small observational studies from the 1970s and 1990s suggest a beneficial clinical and electrophysiological effect in patients with spasticity associated with cerebral palsy and MS.

3. *Diazepam/lorazepam*: see Status epilepticus, pp. 41–5.
4. *Midazolam*: for status epilepticus, evidence for use of midazolam is predominantly extrapolated from children to the adult population. A large meta-analysis of children and young adults ($n = 774$) established that buccal midazolam was both more effective at terminating seizures than rectal diazepam (RR 1.54, 95% CI 1.29–1.85) and could be administered faster (mean difference in time to administration 2.46min).

Dosing and monitoring

1. *Clobazam*: for the treatment of epilepsy, age >12 years—start treatment at 5–10mg/day at night. This can be increased by 5mg/day in weekly intervals. The normal maintenance dose is 20–30mg/day, as either one dose at night or two divided doses with the larger dose at night. The recommended maximum dose is 60mg/day.
2. *Clonazepam*:
   - *epilepsy*: 1mg at night for 4 days. This can be increased over 2–4 weeks to a maintenance dose of 4–8mg. Doses of >4mg/day require bd dosing;
   - *ET/myoclonus/nocturnal spasms/spasticity*: start treatment at 0.5mg at bedtime. Doses can be increased cautiously in 0.5mg increments every 3–4 days to a maximum of 6mg for ET and 4mg for nocturnal spasms. If used as an adjunctive therapy in the treatment of spasticity or in the management of myoclonus, much higher doses of 20mg/day and 15mg/day in 3–4 divided doses has been used in case series (few patients are able to tolerate doses this high);
   - *status epilepticus* (IV): 1mg given over 2min into a large vein. This can be repeated up to three times in 3h;
   - *parasomnia*: recommended doses are between 0.25mg and 2mg at night prior to sleep. This has been increased to 3mg in case studies of non-REM parasomnia and 4mg in case studies of RBD;
   - *RLS*: 0.5–1mg at bedtime is the typical dose.

3. *Diazepam*: within the context of epilepsy, diazepam is predominantly used for status epilepticus where the need for rapid administration is paramount. Oral dosing would mean that maximum plasma levels are attained between 30 and 90min post-dose. Rectal solution (gels are slower) reaches maximum plasma concentration at 10–60min. Hence IV injection is first-line in status epilepticus, and rectal administration used only if IV access is unavailable.
   - IV injection in status epilepticus, age >12 years: 10mg (5mg/mL) given over 1min, and repeated once after 10min, as necessary.
   - Rectal administration as solution in status epilepticus, age >12 years: 10–20mg; repeat once after 10min, as required. Doses limited to 10mg are recommended in the elderly.
4. *Lorazepam*: IV injection in the treatment of status epilepticus, age >12 years—4mg by slow IV infusion, not exceeding 2mg/min. This can be repeated once after 10min, if required. This should be into a large vein to minimize local irritation and thrombophlebitis. In ongoing status, PO or IV maintenance at 4mg, tds to qds, can be continued.
5. *Midazolam*: buccal administration for emergent status epilepticus, age >18 years—10mg, repeated once at 10min, if required.

Therapeutic drug monitoring (rarely required with benzodiazepines)

1. *Clobazam*: optimum seizure control occurs at plasma clobazam levels of 0.03–0.30mg/L and *N*-desmethylclobazam levels of 0.3–3.0mg/L.
2. *Clonazepam*: optimum seizure control when used in monotherapy occurs at plasma concentrations of 0.013–0.070mg/L.
3. *Diazepam*: therapeutic drug monitoring is rarely necessary. Diazepam is primarily intended for use in epilepsy acutely, and not as maintenance therapy. For initial seizure control, plasma levels of ~550ng/mL are recommended.
4. *Lorazepam*: therapeutic drug monitoring is rarely necessary. Lorazepam is primarily intended for use in epilepsy acutely, and not as maintenance therapy. If used as maintenance therapy, optimum seizure control when used as monotherapy occurs at plasma concentrations of 20–30 micrograms/L.
5. *Midazolam*: therapeutic drug monitoring is rarely necessary. Midazolam is primarily intended for use in epilepsy acutely, and not as a maintenance therapy.

Pharmacokinetics and interactions

Pharmacokinetics See Table A.13.

Interactions See Table A.14.

As a rule the benzodiazepines used in epilepsy undergo extensive hepatic metabolism, are eliminated by the renal tract, and do not display autoinduction of liver enzymes.

Diazepam is rapidly and extensively metabolized in the liver to several pharmacologically active metabolites: *N*-desmethyldiazepam, oxazepam, and temazepam. Of these, *N*-desmethyldiazepam can accumulate to levels far in excess of diazepam and contributes to much to the anticonvulsant action of diazepam. Diazepam is circulated around the entero-hepatic system, and, as a result, plasma levels can rise again 6–8h post-dose, as the diazepam is reabsorbed.

Table A.13 Pharmacokinetics of benzodiazepines

	Cloba-zam	Clona-zepam	Diazepam	Lora-zepam	Midazolam	Temazepam
Main routes of admini-stration	PO	IV/PO	IV/PO/PR	IV/PO	Buccal/IV/PO	PO
Oral bioavailability	>95%	>80%	~100%	>90%	75% buccal, <50% oral	~100%
T_{max}	1–3h	1–4h	30–90min PO, 10–60min PR	1.5–2h	0.5–1h PO, 25min buccal	1h
Protein binding	85%	86%	97–99%	90%	96–98%	75–95%
Time to steady state	2–7 days	2–10 days	6–11 days	~3 days	NA	3 days
Distribution half-life	NA	30min	2–13min	<11min	4–19min	1–2h
Pharma-cologically active metabolites	Yes, strong	No	Yes, strong	No	Yes, weak	No
Elimination half-life	10–30h	17–56h	28–54h*	8–24h	1.5–4h	3.5–18h

* Plasma concentrations reduce rapidly initially, with a plasma half-life of ~1h, due to redistribution into adipose tissue.

IV, intravenous; NA, information not available; PO, oral; PR, per rectum.

Table A.14 Interactions of benzodiazepines

Medications which alter benzodiazepine plasma levels	Medications whose plasma levels are altered by benzodiazepines	Pharmacodynamic interactions
Levels decreased: cytochrome P450 inducers, e.g. carbamazepine, cimetidine, phenobarbital, and primidone. Oestrogens and progestogens may also reduce temazepam plasma concentrations **Levels increased:** cytochrome P450 inhibitors, e.g. felbamate, ritonavir, and stiripentol	**Levels increased:** the benzodiazepines may increase plasma levels of carbamazepine, phenytoin, primidone, stiripentol, and valproate	**With CNS depressants, e.g. alcohol, antihistamines, antipsychotics, opioids, and TCAs:** increased sedative effects **With antihypertensives, e.g. ACE inhibitors, α-blockers, etc.:** enhanced hypotensive effects **With levodopa:** levodopa effects may be antagonized

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Carbamazepine and related antiepileptic drugs

Carbamazepine, eslicarbazepine acetate, and oxcarbazepine are most commonly used in the management of focal epilepsy. Carbamazepine is also used first-line in the treatment of trigeminal neuralgia and vestibular paroxysmia, and second-line in the management of rare forms of TACs (SUNCT). The use of carbamazepine is complicated, to some extent, by its side effects and drug interaction profile, due, in part, to its active metabolite carbamazepine-10,11-epoxide. Eslicarbazepine acetate and oxcarbazepine are carbamazepine derivatives. Neither compound is metabolized to carbamazepine-10,11-epoxide. This reduces the risk of liver toxicity and haematological disorders, and means there is little involvement of the cytochrome P450 enzyme system, and thus this decreases the level of autoinduction and interaction with other AEDs. Hence eslicarbazepine acetate and oxcarbazepine have similar actions to carbamazepine and can be used to manage focal epilepsy, and RCTs of oxcarbazepine suggest trigeminal neuralgia when carbamazepine is not tolerated.

Of note, eslicarbazepine acetate has the added benefit that it only requires od dosing, while carbamazepine is the only medication in this group that can be given as a suppository. None of these agents can be given parenterally.

Uses

Licensed uses

In the UK/USA

1. Carbamazepine.
   - *Epilepsy*: carbamazepine is licensed for the treatment of generalized tonic–clonic and focal-onset seizures, with or without secondary generalization, in individuals of all ages.
   - *Trigeminal neuralgia*: carbamazepine is also licensed for the treatment of trigeminal neuralgia in individuals of all ages.
2. Eslicarbazepine acetate.
   - *Epilepsy*: eslicarbazepine acetate is licensed as an adjunct for the treatment of focal-onset seizures, with or without secondary generalization, in individuals aged 16 years and older.
3. Oxcarbazepine.
   - *Epilepsy*: oxcarbazepine is licensed as a monotherapy (UK: age 6 years and older; USA: age 4 years and older) or an adjunct (UK: age 6 years or older; USA: age 2 years and older) for the treatment of focal-onset seizures, with or without secondary generalization.

Off-licence uses

1. *Carbamazepine*: neuropathic pain, SUNCT, and vestibular paroxysmia.

Mechanism of action

The predominant mechanism of action is use-dependent block of neuronal voltage-gated sodium channels. A reduction in glutamate release has also been shown. Carbamazepine may also stabilize neurons by exerting an inhibitory action on L-type calcium channels.

Toxicity and side effects

Many of the side effects are shared within this group of drugs. Theoretically, eslicarbazepine acetate may result in fewer side effects, as peak levels are lower than that of oxcarbazepine.

- *Common—dermatological*: rash is common. Dermatological manifestations are commoner in patients of Han Chinese or Thai origin associated with HLA-B*1502 allele which can be tested for and in whom carbamazepine should be avoided. Skin reactions are less common with eslicarbazepine acetate (1.1%) and oxcarbazepine (5%), compared with carbamazepine (15%). ~25% of patients experiencing a rash with carbamazepine will also experience one with oxcarbazepine. *Endocrine*: carbamazapine and related AEDs share an ADH-like effect, resulting in fluid retention, hyponatraemia, oedema, and weight increase. *Gastrointestinal*: dry mouth, increased γ glutamyl transferase and alkaline phosphatase (ALP), nausea, and vomiting. With carbamazepine suppositories, rectal irritation can occur. *Neurological*: ataxia, blurred vision, diplopia, drowsiness, dizziness, fatigue, and headache are relatively common and most likely due to excessive action at voltage-sensitive sodium channels.
- *Serious—cardiovascular*: arrhythmias and AV block can occur. Thromboembolism and an exacerbation of coronary artery disease has been reported with carbamazepine. *Dermatological*: angio-oedema, Stevens–Johnson syndrome, and toxic epidermal necrolysis have been reported. *Gastrointestinal*: hepatitis and pancreatitis rarely occur. *Haematological*: blood dyscrasias, including aplastic anaemia and pancytopenia, can occur. Exacerbations of porphyria have been seen with carbamazepine. *Immunological*: SLE and a multiorgan hypersensitivity syndrome have also been reported. *Psychiatric*: rarely acute psychosis.

Contraindications

- *Absolute*: these AEDs are ineffective and can even worsen some primary generalized seizure types i.e. absence, atonic, and myoclonic seizures. They should be avoided in patients with AV conduction block. Avoid carbamazepine in patients with porphyria.
- *Relative*: these AEDs should be used with caution in patients with bone marrow depression, open-angle glaucoma, pre-existing hyponatraemia, and heart failure. Carbamazepine should be avoided if the patient has developed previous hypersensitivity reactions to AEDs in this group. Eslicarbazepine acetate and oxcarbazepine should be used with caution if previous hypersensitivity reaction to carbamazepine. Reduced doses should be used in those with hepatic and/or renal impairment. The manufacturers of eslicarbazepine acetate recommend it is avoided in severe hepatic impairment and in renal impairment with an estimated glomerular filtration rate (eGFR) <30mL/min/1.73m^2.

- Eslicarbazepine acetate: if the eGFR is 30–60mL/min/1.73m^2, then the initial dose should be reduced to 400mg on alternate days, increasing to 400mg daily after 1–2 weeks.
- Oxcarbazepine: if the eGFR is <30mL/min/1.73m^2, halve the initial dose, and increments should occur in at least once-weekly intervals.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function and benefit from lower dosing regimens. Pharmacodynamic drug interactions are more likely; the risk of symptomatic hyponatraemia is increased in the elderly who may also take NSAIDs or sodium-lowering antihypertensives.
- *Pregnancy*: for carbamazepine, there is clear evidence, from human studies, of an increased rate of fetal teratogenicity, although this may be minimal, compared to other AEDs. Use in pregnancy involves weighing up the potential benefits and side effects (see Antiepileptic drugs in young women, pp. 37–9). Pregnant patients should be prescribed folic acid throughout pregnancy, and vitamin K prior to birth to reduce the risk of haemorrhage. Elimination of carbamazepine can increase during pregnancy. Total plasma concentration can be reduced by up to 40%. However, for many women, carbamazepine levels may not decline or decline by an average of only 9–12%.

  For eslicarbazepine acetate and oxcarbazepine's side effects in pregnancy have not been adequately explored, although a similar level of teratogenicity to carbamazepine can be expected. Similar precautions to those taken when using carbamazepine are recommended.
- *Lactation*: plasma levels of carbamazepine and oxcarbazepine in infants are 10–20% of that of their mothers (figures for eslicarbazepine acetate are not known). If used, infants should be monitored for potential side effects such as gastrointestinal disturbance, seizures, and respiratory depression. If identified, switch to alternative methods of feeding.

Efficacy

1. Carbamazepine.
   - *Epilepsy*: carbamazepine is one of the most effective drugs used in focal-onset epilepsy. Recent studies demonstrate that it is at least as effective as the newer agents. Its main disadvantage, when compared to other AEDs, e.g. lamotrigine, is the rate of treatment failures due to adverse events. About a third of patients experience symptoms of lethargy and an allergic rash, both approximately twice commoner than in patients initiated on lamotrigine. Five years after starting treatment with carbamazepine as a monotherapy, 45% of patients will enjoy continuing treatment success; 30% of the initial population will have stopped treatment because of side effects, and 25% because of failure of seizure control.
   - *Trigeminal neuralgia*: the majority of data for the efficacy of carbamazepine in trigeminal neuralgia are from small open studies dated from the 1960s. Two RCTs, with the majority of patients suffering from trigeminal neuralgia (98 participants), showed

carbamazepine provided better analgesia than placebo, with an NNT of 2 (95% CI 1–2). It is generally recognized (including by NICE) that there is a lack of good trial evidence for the efficacy of carbamazepine in neuropathic pain. Both the EFNS and NICE recommend carbamazepine first-line for trigeminal neuralgia. The EFNS does not recommend carbamazepine is used for any other type of neuropathic pain disorder.

2. Eslicarbazepine acetate.
   - Eslicarbazepine acetate use in focal-onset seizures has been the subject of a recent Cochrane review. It concluded that, as an adjunct, eslicarbazepine acetate can reduce seizure frequency in the short term. However, there are little data on longer-term outcomes. A further integrated analysis of three phase 3, double-blind, placebo-controlled studies in patients with focal-onset epilepsy refractory to up to three medications showed that over a third of patients can experience at least a 50% reduction in seizure frequency when eslicarbazepine acetate is used as an adjunct.
3. Oxcarbazepine.
   - A multinational, multicentre, double-blind trial investigated the effectiveness of oxcarbazepine in refractory focal epilepsy. It demonstrated a reduction in seizure frequency in 40% at doses of 1.2g and 50% at doses of 2.4g daily. The frequency of rash with oxcarbazepine is two-thirds lower than with carbamazepine.

Dosing and monitoring

Dosing

1. *Carbamazepine (all indications)*: start treatment at 100–200mg od to bd, and increase every 1–2 weeks by 100–200mg in divided doses. The sustained-release preparations require bd dosing, and the normal preparations three divided daily doses. For epilepsy, the dose in adults is normally titrated up to about 800–1200mg/day, although this can go up to 2g/day, if required. For other indications, the usual maintenance dose is 600–800mg/day.
2. *Eslicarbazepine acetate*: start treatment at 400mg od (tablets will need to be split). The tablets can be increased by 400mg increments 1- to 2-weekly up to 1.2g, although 800mg is normally a sufficient maintenance dose.
3. *Oxcarbazepine (all indications)*: start treatment at 300mg bd; increase weekly in steps of up to 600mg to a maximum dose of 2.4g. The usual daily dosage range in adults is between 0.6g and 2.4g in two divided doses.

Routine monitoring

- *Carbamazepine*: prior to initiation of treatment, FBC, and renal and liver function should be assessed. An FBC is recommended 2-weekly for 2 months, then 3-monthly throughout treatment. Liver and renal function should be assessed 6- to 12-monthly throughout treatment.
- *Eslicarbazepine acetate/oxcarbazepine*: before initiation of treatment, liver and renal function tests are recommended. These should be repeated yearly.

Therapeutic drug monitoring

- Optimum seizure control when used in monotherapy for carbamazepine occurs at plasma concentrations of 4–12mg/L, and for eslicarbazepine acetate and oxcarbazepine at 3–35mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

Oxcarbazepine and eslicarbazepine acetate are both prodrugs which are converted to eslicarbazepine in the liver.

1. *Carbamazepine*: oral bioavailability of carbamazepine is ~85%. Peak plasma concentrations are reached at different time points, depending on the formulations used: conventional tablets at ~12h, chewable tablet at ~6h, and liquid at ~2h. This is not affected by food co-ingestion. Bioavailability varies between preparations. Due to reduced bioavailability, a 125mg suppository is equivalent to a 100mg oral tablet. Steady-state plasma concentrations are reached within 1–2 weeks, depending on autoinduction of cytochrome P450 enzymes and interaction with other AEDs. 70–80% of carbamazepine is bound to plasma protein. Carbamazepine is metabolized by the liver into a number of derivatives, including the pharmacologically active carbamazepine-10,11-epoxide. The metabolites are then excreted ~70% in the urine and ~30% in the stool. The half-life varies with duration of therapy. At initiation, the half-life is 36h; after a few weeks, hepatic enzyme autoinduction means that the half-life decreases to 16–24h.
2. *Eslicarbazepine acetate*: eslicarbazepine acetate is a prodrug, rapidly converted by hepatic first-pass metabolism to the active metabolite eslicarbazepine. The bioavailability is >90%, and T_{max} occurs 2–3h post-dose. The half-life of eslicarbazepine acetate is 2h; that of the active metabolite eslicarbazepine is 20–24h. A third of eslicarbazepine is conjugated with glucuronic acid in the liver. The majority of the rest is excreted unchanged; >90% is excreted renally.
3. *Oxcarbazepine*: oral bioavailability is ~100%. T_{max} occurs 3–6h post-dose. This is rapidly metabolized by the liver into its active metabolite 10-hydroxycarbazepine (also known as eslicarbazepine), which, in turn, reaches its steady-state plasma level in 2–3 days. 10-hydroxycarbazepine is metabolized by conjugation with glucuronic acid in the liver, and, unlike with carbamazepine, there is no autoinduction; hence pharmacokinetics are linear. The half-life of oxcarbazepine is 2h, and that of 10-hydroxycarbazepine 8–15h. Over 95% of the drug and its metabolites are excreted in the urine.

Interactions See Table A.15.

Table A.15 Interactions of carbamazepine and related AEDs

Medications which alter AED plasma levels	Medications whose plasma levels are altered by AED	Pharmacodynamic interactions
1. Carbamazepine **Levels decreased:** CYP3A4 inducers, e.g. oxcarbazepine and rifampicin **Levels increased:** CYP3A4 inhibitors, e.g. cimetidine, clarithromycin, and fluconazole **2. Eslicarbazepine acetate** **Levels decreased:** carbamazepine, phenytoin, and topiramate **3. Oxcarbazepine** **Levels decreased:** carbamazepine, lacosamide, oral contraceptives, phenobarbital, phenytoin, and verapamil **Levels increased:** viloxazine	**1. Carbamazepine** **Levels decreased:** CYP3A4 substrates, e.g. amitriptyline, benzodiazepines, ketoconazole,* and quetiapine* **Levels increased:** verapamil **2. Eslicarbazepine acetate** **Levels decreased:** lamotrigine, topiramate, valproate, and warfarin **Levels increased:** phenytoin **3. Oxcarbazepine** **Levels decreased:** carbamazepine, felodipine, lamotrigine, levetiracetam, rufinamide, and topiramate **Levels increased:** phenobarbital and phenytoin	**1. Carbamazepine with lamotrigine and levetiracetam:** headache, nausea, and ataxia **2. Eslicarbazepine acetate:** nil **3. Oxcarbazepine** **With lithium and lamotrigine:** enhanced neurotoxicity

* As a result of the magnitude of the interaction between carbamazepine and ketoconazole and between carbamazepine and quetiapine whereby ketoconazole and quetiapine plasma levels are decreased to almost non-detectable values, these drug combinations can be considered contraindicated.

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Catechol-*O*-methyltransferase inhibitors

COMT inhibitors have been used in the treatment of PD since the mid 1990s. They include entacapone and tolcapone. The latter is used second-line due to the rare, but significant, risk of severe liver dysfunction. COMT inhibitors are used as an adjunct to levodopa therapy, particularly in patients with motor fluctuations, as they may improve the wearing-off phenomenon and may also permit a reduction in the required levodopa dose.

Uses

Licensed uses

In the UK/USA

- *PD*.
  1. *Entacapone* is licensed as an adjunct to levodopa for the treatment of end-of-dose motor fluctuations in patients with PD in individuals aged 18 years and older.
  2. *Tolcapone* is licensed for use as an adjunct to levodopa therapy in patients with levodopa-responsive PD who are intolerant of, or have failed to show improvement with, an alternative COMT inhibitor in individuals aged 18 years and older.

Off-licence uses

- None.

Mechanism of action

When levodopa is taken with a peripheral dopa-decarboxylase inhibitor, metabolism by COMT (found in the liver, gastrointestinal tract, and erythrocytes) becomes the major pathway of levodopa metabolism. Selective reversible inhibition of peripheral COMT by entacapone and tolcapone results in increased bioavailability of levodopa by preventing conversion to 3-*O*-methyldopa and provides increased dopaminergic input to the striatum. As well as inhibiting peripheral COMT, tolcapone also acts to inhibit central COMT; the significance of this is unclear.

Toxicity and side effects

- *Common—cardiovascular*: orthostatic hypotension and syncope. *Gastrointestinal*: abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, gastritis, nausea, taste disturbance, and vomiting. *Genitourinary*: urine discoloration (red-brown). *Neurological*: dizziness, dyskinesia (managed with 10–30% reduction in levodopa dose), hallucinations, somnolence, and weakness. *Respiratory*: dyspnoea.
- *Serious—gastrointestinal*: abnormal LFTs (rarely fulminant hepatic failure with tolcapone) retroperitoneal fibrosis. *Musculoskeletal*: rhabdomyolysis. *Neurological*: neuroleptic malignant-like syndrome on withdrawal. *Respiratory*: pulmonary fibrosis.

Patients may experience increased dopaminergic side effects (e.g. dyskinesia, postural hypotension, etc.), due to the increased serum concentration of levodopa. Reduction in levodopa dose may help in this instance.

Contraindications

- *Absolute*: known hypersensitivity to COMT inhibitor, severe liver disease, phaeochromocytoma, previous NMS, and rhabdomyolysis.
- *Relative*: concurrent non-selective MAOI use due to theoretical risk of excess catecholinergic activity. No dosage alteration is required in renal impairment. Monitor closely in cases of mild to moderate hepatic impairment, although no dose alteration is routinely recommended.

Uses in special populations

- *Elderly*: no dose adjustment is routinely required.
- *Pregnancy*: animal reproduction studies report adverse events. There is a lack of safety data for use in pregnancy. The manufacturers advise avoidance, where possible, in this patient group.
- *Lactation*: excretion in breast milk is not known. The manufacturers advise avoidance, where possible, in nursing mothers.

Efficacy

- *Entacapone*: STRIDE-PD (STalevo Reduction in Dyskinesia Evaluation) was a double-blind RCT comparing the effect of Stalevo® (levodopa/carbidopa/entacapone) to levodopa/carbidopa in patients with early PD who had not previously been treated with levodopa and did not have motor complications. Although outcomes were improved in both groups (UPDRS-II and III), no significant difference was noted between the groups. The LARGO (Lasting effect in Adjunct therapy with Rasagiline Given Once daily) study was a double-blind RCT ($n = 687$) which randomized patients to rasagiline (1g/day), entacapone (200mg with each levodopa dose), or placebo over an 18-week period. Thirteen per cent of patients did not complete the study, due to withdrawal of consent and adverse events. The trial showed a significant increase in 'on' time in both rasagiline and entacapone arms (0.85h vs placebo 0.03h; $p = 0.0005$) and reduction in 'off' time (−1.18h rasagiline and −1.2h entacapone vs placebo −0.4h; $p = 0.0001$, $p < 0.0001$, respectively).

  The MDS review found entacapone efficacious as a symptomatic adjunct to levodopa only in patients with motor fluctuations. There is no evidence that use early in the disease course prevents or delays motor complications.
- *Tolcapone*: a double-blind, placebo-controlled trial of tolcapone as an adjunct to levodopa ($n = 298$) found the treatment group had a significant reduction in levodopa usage and improvement in motor scores (100mg tds, $p < 0.05$; 200mg tds, $p < 0.01$). Activities of daily living, as part of the UPDRS, was the primary outcome measure and was found to have significant improvements from baseline in both tolcapone groups, compared to placebo ($p < 0.01$). Greatest effect was noted in those with most severe impairment at baseline. The most important non-dopaminergic side effect was diarrhoea.

  The MDS review found tolcapone efficacious as a symptomatic adjunct to levodopa only in patients with motor fluctuations. There is no evidence that use early in the disease course prevents or delays motor complications.

Dosing and monitoring

- *Entacapone*: start treatment at 200mg, taken with each levodopa dose. Maximum 2g/day (ten tablets). Levodopa dose often needs to be reduced by approximately one-third, or the dosing interval may need to be extended.
- *Tolcapone*: start treatment at 100mg tds. Only in exceptional circumstances can this be increased to 200mg tds. If there is no clinical benefit within 3 weeks, it should be stopped.

Routine monitoring

- *Entacapone*: routine monitoring of liver function is not necessary.
- *Tolcapone*: LFTs are measured every 2 weeks for the first year of treatment, 4 weeks for the next 6 months, and every 8 weeks thereafter.

Pharmacokinetics and interactions

Pharmacokinetics See Table A.16.

Interactions See Table A.17.

Table A.16 Pharmacokinetics of COMT inhibitors

	Entacapone	Tolcapone
Main routes of administration	PO	PO
Oral bioavailability	35%	65%
T_{max}	1h	2h
Protein binding	98%	99.8%
Time to steady state	2–7 days	2–10 days
Metabolism	Hepatic CYP2C9	Hepatic
Pharmacologically active metabolites	Yes (*cis*-isomer)	No
Elimination half-life	3h	2–3h
Elimination routes	80–90% faeces 10–20% urine	40% faeces 60% urine

Table A.17 Interactions of COMT inhibitors

Medications which alter COMT inhibitor plasma levels	Medications whose plasma levels are altered by COMT inhibitors	Pharmacodynamic interactions
Levels decreased: iron (oral) with entacapone	**Levels increased:** warfarin with entacapone	**With other CNS depressants:** may increase risk of CNS depression **Caution advised with MAOIs, TCAs, SNRIs, and drugs metabolized by COMT, e.g. adrenaline:** limited experience with these drugs (selegiline can be used, but maximum dose 10mg)

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Corticosteroids

Corticosteroids (CS) are hormones synthesized from cholesterol in the adrenal cortex. They have diverse physiological and molecular effects on the body. They can be broadly divided into two classes—glucocorticoids (GCs), which control carbohydrate and fat metabolism, and mineralocorticoids (MCs) which principally regulate sodium balance (see Table A.18). The anti-inflammatory properties of GCs are exploited in neurology, and there are several empirical and evidence-based uses in the field. Far from being a panacea for neurological disease, GCs often form part of complex immunosuppressive treatment regimens. Unfortunately, their diverse side effect profile limits their long-term use.

Several qualitative and clinically relevant differences exist between CS. Cortisol is made by the zona fasciculata of the adrenal cortex and is the active endogenous GC. This is metabolized to cortisone which is largely inactive. Hydrocortisone is the synthetic form of cortisol and is used IV on a short-term basis for emergency management of inflammatory conditions. Prednisolone is the most commonly administered oral steroid. It is the active metabolite of prednisone (itself inactive) and is used for long-term disease suppression. Methylprednisolone is often used as IV pulsed therapy for suppression of inflammatory disorders, e.g. MS. Dexamethasone possesses negligible MC activity therefore is highly useful in clinical situations in which fluid retention would be deleterious. Aldosterone is the active endogenous MC, and fludrocortisone is its synthetic, exogenously administered analogue. For comparison of relative GC and MC effects of commonly used CS, see Table A.18.

Table A.18 Relative glucocorticoid (GC) and mineralocorticoid (MC) effects of commonly used corticosteroids

Drug	GC effect	MC effect	Anti-inflammatory dose equivalent to 5mg prednisolone
Hydrocortisone	1	1	20mg
Prednisolone	4	0.8	5mg
Methylprednisolone	5	–	4mg
Dexamethasone	30	–	750 micrograms
Fludrocortisone	10	125	NA

NA, information not available.

Uses

1. *Methylprednisolone and prednisolone*: the uses of methylprednisolone and prednisolone are very broad. In general, IV pulsed methylprednisolone is used acutely for any condition in which a rapid and intense CS effect is required. Oral prednisolone is used in the management of all conditions deemed likely to benefit from short- or long-term GC therapy:
   - ADEM;
   - autoimmune limbic encephalitis;
   - Behçet's;
   - Bell's palsy;

- CIDP;
- DMD;
- GCA;
- IBM (trial);
- LEMS;
- MOH;
- MS;
- MG;
- neurolupus;
- NMO;
- neurosarcoidosis;
- optic neuritis;
- PM/DM;
- Sjögren's syndrome;
- Susac's syndrome;
- TACs;
- TM;
- status migrainous;
- vasculitis.

2. *Dexamethasone*.

Licensed uses

In the UK/USA

- *Cerebral oedema*: in the UK, dexamethasone is licensed for use as an adjunct in the control of raised ICP secondary to cerebral tumours and infantile spasms in individuals of all ages. In the the USA, it is licensed for use in the management of cerebral oedema associated with primary or metastatic brain tumour, craniotomy, or head injury in individuals of all ages.

Off-licence uses

- Adjunctive treatment in acute bacterial meningitis and VZV encephalitis.

3. Fludrocortisone

See further information on pp. 465–6.

Mechanism of action

- *Neuro-inflammatory conditions*: the anti-inflammatory properties of GCs arise through multiple mechanisms; they bind to intracellular cytoplasmic receptors, inducing a range of cellular responses, including modification of transcription and protein synthesis. This leads to modulation of leucocyte activation, migration, cytokine production, and overall suppression of humoral responses.
- *Cerebral oedema*: dexamethasone reduces cerebral oedema formation by upregulation of cell membrane tight junctions, thereby reducing endothelial permeability at the blood–brain barrier. Several mediators are thought to be involved via steroid–receptor complex effects on gene transcription. These include downregulation of VEGF production, phospholipase A2 inhibition, and stabilization of lysosomal membranes.

Toxicity and side effects

Short courses of steroids are typically associated with minor and transient side effects. These include dyspepsia, sleep disturbance, mood changes, confusion, infection risk, and impaired glucose tolerance. Repeated courses, higher doses, and chronic use are associated with the following side effects:

- *Common—cardiovascular*: hypertension. *Dermatological*: acne, ecchymosis, impaired healing, and skin atrophy. *Endocrine*: Cushingoid appearance, hypokalaemia, impaired glucose tolerance,

increased appetite, sodium and water retention, and weight gain. *Gynaecological*: menstrual irregularity. *Haematological*: leucocytosis. *Immunological*: hypersensitivity and increased susceptibility to infections. *Musculoskeletal*: osteoporosis and proximal myopathy. *Ophthalmological*: subcapsular cataracts. *Psychiatric*: affective disorder.

- *Serious—cardiovascular*: deterioration in cardiac failure. *Dermatological*: Kaposi's sarcoma. *Endocrine*: adrenal insufficiency on withdrawal of treatment. *Gastrointestinal*: gastrointestinal ulceration and pancreatitis. *Musculoskeletal*: avascular necrosis of the hip is an important, but rare, potential side effect, which can occur after a single course. *Immunological*: anaphylaxis, increased susceptibility to infections, and reactivation of latent TB. *Neurological*: increased risk of seizures. *Ophthalmological*: glaucoma. *Psychiatric*: psychosis and suicidal ideation.

Dexamethasone has a lower propensity to cause psychosis but is more likely to cause steroid myopathy and weakness due to its fluorinated chemical composition. IV administration of dexamethasone is associated with perineal paraesthesiae, beginning within seconds of dose commencement and clearing soon after stopping. This is thought to be a chemical effect of the CS phosphate ester and can be avoided by administering the drug in a more dilute form or more slowly.

Contraindications

- *Absolute*: hypersensitivity and systemic infections (unless with concurrent anti-infective treatments).
- *Relative*: live virus vaccines (e.g. measles, VZV). In hepatic and renal impairment, caution is advised with the use of CS, due to increased risk of fluid retention in these patients.

Uses in special populations

- *Elderly*: age-related impairment of renal and hepatic function is commoner in the elderly. In addition, side effects, including osteoporosis, hypertension, hypokalaemia, diabetes, skin thinning, and infection, may be more severe in the elderly. These patients require frequent monitoring for complications, and lower dosing may be necessary.
- *Pregnancy*: there is weak evidence of an increased risk of cleft palate or lip in the fetus with maternal CS use, and prolonged use may lead to intrauterine growth retardation. CS have a very low teratogenic potential but may cause transient adrenal suppression in the neonate. Generally, however, the risks of CS use in pregnancy are far outweighed by the benefits to the mother, especially in active inflammatory or immune-mediated disease.
- *Lactation*: prednisolone is excreted into breast milk. Although doses of <40mg/day are unlikely to cause systemic effects in the infant, it is recommended that adjustments are made to the dosing interval to allow 4h before breastfeeding.

Efficacy

1. *Methylprednisolone and prednisolone* are used to treat a large number of autoimmune and inflammatory conditions. For a list of uses, see p. 306. For a discussion of the evidence base for its use in these indications, see the individual conditions.
2. *Dexamethasone*.
   - *Acute bacterial meningitis*: dexamethasone reduces the risk of severe hearing loss and short-term neurologic sequelae in bacterial meningitis by 33% and 17%, respectively. It does not affect overall mortality, but subgroup analysis has shown that it reduces mortality in meningitis caused by *S. pneumoniae* (RR 0.84, 95% CI 0.72–0.98). It is associated with an increase in recurrent fever, but not in other adverse events.
   - *Cerebral oedema associated with malignancy*: there is a paucity of high-quality evidence showing that dexamethasone improves prognosis in cerebral oedema associated with malignancy. Nonetheless, up to 75% of patients treated with dexamethasone show neurological improvement at 48h, and practical guidelines provide low-level recommendations of use, based on symptom severity. The practice is now widespread.

Dosing and monitoring

Dosing

1. *Dexamethasone*.
   - *Bacterial meningitis*: start treatment before or with the first antibiotic dose: 0.15mg/kg every 6h for 4 days. This can be stopped earlier if an alternative organism to *S. pneumoniae* is identified.
   - *Cerebral oedema*: the dosage of dexamethasone used in the management of brain tumour-related cerebral oedema depends upon the speed of onset and severity of symptoms. In the acute, unstable situation, dexamethasone can be given by IV injection at 8–16mg; then 5mg may be given by IM or IV injection 6-hourly thereafter for 2–4 days, prior to taper. In a more stable situation with slow onset of symptoms, dexamethasone can be given by oral tablets in doses of 2–6mg bd to qds, with or without a higher loading dose of 4–16mg, depending on symptom severity. Dexamethasone should be withdrawn as rapidly as feasible, although in some patients with widespread cerebral oedema or particularly aggressive tumours, a slower taper may be required. In patients with good performance status, then taper by 50% every 4 days, aiming to complete withdrawal in 2–3 weeks. In those with a worse clinical condition, then taper more slowly, e.g. reduction by 25% every 7–8 days, and a low level of maintenance dexamethasone may be required to prevent return of symptoms.
2. Methylprednisolone.
   - A wide range of dosing regimens can be used. Three days of daily IV doses of 1000mg methylprednisolone or 5 days of daily PO doses of 500mg methylprednisolone are commonly used for acute

exacerbations of MS and other acute inflammatory conditions. In the context of an acute MS relapse some clinicians employ a short taper of prednisolone, following IV methylprednisolone, although there is no evidence base to support this practice.

3. *Prednisolone*.
   - See individual conditions for the usual dose. The general principles are that prednisolone can be started at high doses of 1mg/kg od, but a maximum dose of 60mg is recommended for most conditions. MG is a notable exception to this regimen where a low dose on alternate days is gradually titrated upwards to avoid the 'steroid dip' in symptoms seen 4–10 days after starting high doses. Such high doses can be used in the longer term in some conditions but are usually tapered after the first week or month. This typically involves dose reductions of 10mg/week, until a daily dose of 30mg is reached. Reductions of 2.5mg can then be made every 1–2 weeks, until a daily dose of 10mg is reached, after which 1mg decrements may be needed. This taper may need to be titrated to symptoms, and slower decrements of 1mg/month may be initially needed in certain conditions such as neurosarcoidosis.

Monitoring

Patients should be monitored for the development of common side effects noted above, with provisions made to reduce the total steroid dose as soon as possible with steroid-sparing anti-inflammatory medications. In patients on high-dose steroids, consideration should be given to the co-prescription of medications for bone and gastric protection. If GCs have been administered for <3 weeks, treatment can be ceased without tapering. Tapering doses of GCs are required for longer, higher-dose (>40mg/day prednisolone), or repeated treatment courses or in patients who may have adrenal suppression from another cause.

Pharmacokinetics and interactions

Pharmacokinetics See Table A.19.

Interactions See Table A.20.

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Table A.19 Pharmacokinetics of corticosteroids

	Hydrocortisone	Prednisolone	Methyl-prednisolone	Dexa-methasone
Main routes of administration	IV, PO	PO	IV, PO	IV, PO
Onset of action (h)	IV: immediate; PO: 1–2	Unknown	IV: immediate; PO: 1–6	IV: 1; PO: unknown
Duration of action (h)	8–12	12–36	12–36	36–72
Oral bioavailability	96%	99%	88%	76%
T_{max} (h)	1.2	1.3	0.8	1.5
Protein binding	92%	86%	79%	77%
Metabolism	Hepatic glucuronidation and sulfate conjugation			
Excretion	Renal (<20% as unchanged drug)			
Elimination half-life (min)	80–115	150–210	78–188	190

IV, intravenous; PO, oral.

Table A.20 Interactions of corticosteroids (CS)

Medications which alter CS plasma levels	Medications whose plasma levels are altered by CS	Pharmacodynamic interactions
Levels decreased: carbamazepine, phenobarbital, phenytoin, rifampicin, primidone **Levels increased:** aprepitant (MP), asparaginase (dex), ciclosporin, diltiazem (MP), erythromycin, itraconazole, ketoconazole, oral contraceptives containing oestrogen, ritonavir and related protease inhibitors	**Levels decreased:** aspirin, axitinib (dex), aquinavir (dex), calcium salts, caspofungin (dex), cobicistat (dex), elvitegravir (dex), indinavir (dex), isoniazid, lopinavir (dex), phenytoin (dex), rilpivirine (dex), sodium benzoate, sodium phenylbutyrate, telaprevir (dex), ticagrelor (dex), triazolam (dex) **Levels increased:** ciclosporin, phenytoin (dex)	**With antihyperglycaemics, antihypertensives, and pancuronium/vecuronium:** antagonizes hypotensive, hypoglycaemic, and muscle relaxant effects **With aspirin and NSAIDs:** increased risk of gastrointestinal bleeding **With drugs causing hypokalaemia, e.g. diuretics, β-agonists:** increased risk of hypokalaemia **With warfarin:** increased anticoagulant effect **With mifepristone:** reduced CS effect **With aldesleukin and mifamurtide:** reduced antineoplastic effect **Dexamethasone with lenalidomide/thalidomide:** increases thrombogenic effects when used in combination as chemotherapy for multiple myeloma

dex, dexamethasone; MP, methylprednisolone.

Ergot-based dopamine agonists

DAs were first introduced as a treatment for PD in the 1970s. Bromocriptine was synthesized in 1965, and other ergot-based DAs soon followed (cabergoline, pergolide, and lisuride). Due to the risk of fibrosis (retroperitoneal, cardiac, and pulmonary), ergot-based DAs are now only rarely used in the treatment of PD. Non-ergot DAs (apomorphine, pramipexole, ropinirole, and rotigotine) are preferred, due to their safer side effect profile.

Uses

Licensed uses

In the UK/USA

- PD.
  1. *Bromocriptine*: is licensed for the treatment of idiopathic PD (USA: and post-encephalitic parkinsonism) as a monotherapy or an adjunct to levodopa. It can be used first-line in previously untreated patients, in patients with disabling on–off phenomena, to reduce the dose of levodopa and hence minimize associated side effects, and in those with poor or declining response to levodopa, in individuals aged 7 years and older in the UK, and those aged 16 years and older in the USA.
  2. *Cabergoline* (UK only): is licensed for use as a second-line therapy for the management of patients with PD who are intolerant of, or fail, treatment with a non-ergot compound, as a monotherapy or as adjunctive treatment to levodopa in individuals aged 18 years and older.

Cabergoline is not licensed for the management of PD in the USA.

Off-licence uses

1. *Bromocriptine*: NMS/PHS and RLS.
2. *Cabergoline*: RLS.

Mechanism of action

The predominant mechanism of action for this group of drugs is through activation of post-synaptic dopamine receptors to restore nigrostriatal dopaminergic output. Bromocriptine and cabergoline are long-acting agonists selective for D2 receptors, having no significant affinity at D1 receptors. Bromocriptine is also an agonist at serotonergic receptors (5HT1 and 5HT2).

Toxicity and side effects

- *Common—cardiovascular*: digital vasospasm, orthostatic hypotension, Raynaud's phenomenon, and syncope. *Endocrine*: hypoglycaemia. *Gastrointestinal*: abdominal pain, constipation, diarrhoea, dry mouth, nausea, and vomiting. *Neurological*: drowsiness, dizziness, headache, and somnolence. *Psychiatric*: anxiety and depression. *Respiratory*: nasal congestion, flu-like symptoms, and sinusitis.
- *Serious—cardiovascular*: arrhythmia, constrictive pericarditis, hypertension, MI, pericardial effusion, peripheral oedema, syncope, valvular fibrosis, and ventricular tachycardia. *Gastrointestinal*: dysphagia,

gastrointestinal ulcer, gastrointestinal haemorrhage, and retroperitoneal fibrosis. *Neurological*: increased CSF pressure, paraesthesiae, seizure, and sudden-onset sleep (patients should be counselled and advised not to drive if experiencing this side effect). *Psychiatric*: depression, ICDs, and psychomotor agitation.

Contraindications

- *Absolute*: hypersensitivity to ergot alkaloids; unstable coronary artery disease and peripheral vascular disease; uncontrolled hypertension, hypertensive disorders of pregnancy (including eclampsia, pre-eclampsia, or pregnancy-induced hypertension), hypertension post-partum and in the puerperium, and pulmonary fibrosis.
- *Relative*: abnormal liver function may result in reduced clearance and accumulation requiring dose reduction. No dose alteration is required in renal impairment.

Uses in special populations

- *Elderly*: no dose alterations are routinely required.
- *Pregnancy*: teratogenic effects were not noted in animal studies. Limited data show no increase in congenital malformations in early pregnancy. Bromocriptine is favoured for the treatment of prolactinoma in pregnancy. Available data on women taking bromocriptine during pregnancy (for prolactinoma) did not show adverse outcomes. However, use in pregnancy is not advised unless for treatment of prolactinoma.
- *Lactation*: bromocriptine is secreted into breast milk and inhibits lactation; it is unclear if cabergoline behaves in a similar fashion. The manufacturers advise avoidance in nursing mothers, where possible.

Efficacy

1. *Bromocriptine*: a large meta-analysis ($n = 5247$ patients) of the use of ergot- and non-ergot-based DAs in early PD found that patients were less likely to develop motor complications (dyskinesia, dystonia, and motor fluctuations) with DAs than levodopa; however, there was a greater incidence of other non-motor side effects (oedema, constipation, somnolescence, dizziness, nausea, and hallucinations). Patients treated with DAs were also more likely to discontinue treatment. A 10-year follow-up study found that bromocriptine in early PD did not reduce mortality or motor disability. The initial reduced frequency in motor complications was not sustained.
2. *Cabergoline*: a double-blind RCT, which investigated the use of levodopa ($n = 211$) or cabergoline ($n = 209$) in early PD patients over the course of 5 years, found that cabergoline delayed the onset and frequency of motor complications. The final average cabergoline dose was 2.9mg, with 431mg of supplemental levodopa, compared with 784mg of levodopa alone. The MDS review concluded that cabergoline is efficacious as a symptomatic monotherapy, as an adjunct to levodopa, and as treatment to prevent/delay motor complications (fluctuations and dyskinesias).

Dosing and monitoring

1. *Bromocriptine*.
   - *PD*: start treatment at 1–1.25mg at night; at 1 week, increase to 2–2.5mg at night; at 2 weeks, increase to 2.5mg bd, then to 2.5mg tds a week later. This can be increased by a further 2.5mg daily every 3–14 days, according to clinical response, to a usual range of 10–30mg daily.
   - *NMS*: give at a dose of 2.5mg every 6–8h, and continue for 10 days after NMS becomes well controlled. Subsequent gradual reduction, with monitoring for relapse of symptoms or rising CK.
2. *Cabergoline*: start treatment at 0.5mg/day, and increase by 0.5mg every 2 weeks. Maximum dose 2–4mg. Maximum dose 6mg/day.

Routine monitoring

See ergot-based DAs.

Regular review for the presence of ICDs, DAWS, sudden-onset sleep attacks, and ergot-associated fibrotic side effects is advised with auscultation for cardiac murmurs and pulmonary fibrosis. Regular monitoring by CXR, ECG, echocardiogram, ESR, and renal function is needed in those on long-term treatment.

Pharmacokinetics and interactions

Pharmacokinetics See Table A.21.

Interactions See Table A.22.

Table A.21 Pharmacokinetics of ergot-based DAs

	Bromocriptine	Cabergoline
Main routes of administration	PO	PO
Oral bioavailability	<10%	Unknown
T_{max}	1–3h	0.5–4h
Protein binding	96%	40–42%
Time to steady state	10 days	4 weeks
Metabolism	CYP3A4	CYP3A4
Pharmacologically active metabolites	Yes	Yes
Elimination half-life	2–8h	63–68h
Elimination routes	82% faeces 6% urine	60% faeces 22% urine

Table A.22 Interactions of ergot-based DAs

Medications which alter ergot-based DA plasma levels	Medications whose plasma levels are altered by ergot-based DAs	Pharmacodynamic interactions
Levels increased: CYP3A4 inhibitors, e.g. protease inhibitors, macrolides, and azole antifungals	**Levels increased:** CYP3A4 substrates, e.g. statins and TCAs	**With sympathomimetics such as pseudoephedrine:** can cause psychosis or cardiac arrhythmias (ventricular tachycardia) (rare)
Levels decreased: CYP3A4 inducers, e.g. carbamazepine, dexamethasone, and phenytoin		**With antihypertensives:** can worsen orthostatic hypotension
		With tramadol, trazodone, and other serotonergic agonists: may increase the risk of serotonin syndrome

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Monoamine oxidase inhibitors

MAOIs are used as an adjunct in the management of PD. They are typically used later in the disease course to minimize the use of levodopa and hence reduce motor side effects of levodopa treatment. Early MAOIs were non-selective in their action, inhibiting monoamine oxidase A (MAO-A) and B. Their inhibition of MAO-A, an isoenzyme responsible for tyramine, adrenaline, noradrenaline, serotonin, and dopamine metabolism, meant that their use was limited by the hypertensive 'cheese reaction' whereby ingestion of tyramine, as found in cheese, led to marked elevation in tyramine and catecholamines, leading to hypertension. The MAO-B enzyme mainly metabolizes dopamine and has little role in metabolism of other catecholamines, and hence, with newer MAO-B selective inhibitors, the 'cheese reaction' should not occur. The phenomenon can still occur with selegiline, due to some MAO-A inhibition at higher doses, but not with rasagiline where there is little MAO-A inhibition.

Uses

Licensed uses

In the UK/USA

- *PD*.
  1. *Rasagiline* is licensed for the treatment of idiopathic PD as monotherapy or as adjunct therapy with levodopa in individuals aged 18 years and older. In the UK, the licence is restricted to patients with end-of-dose fluctuations.
  2. *Selegiline* is licensed as an adjunct to levodopa therapy in the management of PD, specifically for the treatment of fluctuating motor symptoms, including dyskinesias, and 'end-dose' and 'on–off' phenomena in individuals aged 18 years and older.

Off-licence uses

- None.

Mechanism of action

Rasagiline and selegiline are selective irreversible inhibitors of MAO-B. MAO-B metabolizes dopamine and phenylethylamine. Inhibition results in increased synaptic concentration of dopamine within the PNS and CNS.

Toxicity and side effects

- *Common—cardiovascular*: hypotension (including postural). *Gastrointestinal*: abdominal pain, diarrhoea, dry mouth, dyspepsia, nausea, and stomatitis. *Neurological*: confusion, dizziness, dyskinesia, hallucinations, headache, insomnia, and vivid dreams.
- *Serious—cardiovascular*: arrhythmias. *Psychiatric*: psychosis. *Systemic*: serotonin syndrome and tyramine-induced hypertensive crisis.

Contraindications

- *Absolute*: hypersensitivity to MAOIs, severe liver disease, active peptic ulcer disease, concomitant use of other MAOIs, SSRIs (e.g. fluoxetine—5-week washout period advised), and pethidine.
- *Relative*: no dosage adjustment in renal and hepatic impairment. Use with caution in severe impairment.

Uses in special populations

- *Elderly*: no dose adjustment is routinely required.
- *Pregnancy*: adverse events were observed in some animal reproduction studies. The manufacturers advise avoidance, if possible, in this group.
- *Lactation*: inhibition of prolactin secretion may inhibit lactation. Excretion in breast milk unknown; hence, as a precaution, the manufacturers advise avoiding use in nursing mothers.

Efficacy

- *Rasagiline*: there is a good evidence base from several RCTs that rasagiline is effective as both a monotherapy and an adjunct in the management of PD. For example, the *TEMPO* study (TVP-1012 in Early Monotherapy for PD Outpatient trial), an RCT of rasagiline use in levodopa-naïve early PD patients ($n = 404$), lasting 26 weeks, demonstrated that, at 1mg, there was a reduction of 4.20 units in the UPDRS score, compared to placebo (95% CI −5.66 to −2.73 units; $p < 0.001$), and, at 2mg, a reduction of 3.56 units (95% CI −5.04 to −2.08 units; $p < 0.001$).

  Researchers have suggested that rasagiline may also have a neuroprotective effect, based on its antiapoptotic and antioxidant activity. The *ADAGIO* (Attenuation of Disease Progression with Azilect Given Once-daily trial) RCT used a delayed-start design to assess whether rasagiline has disease-modifying properties in early untreated PD. Phase 1 lasted 36 weeks and assigned patients to either rasagiline 1mg, 2mg (the early-start groups), or placebo. In phase 2, the early-start groups continued their assigned treatments, and the placebo groups were randomly assigned to either 1mg or 2mg rasagiline. The trial suggested there was a beneficial neuroprotective effect of early treatment with rasagiline, compared to delayed treatment, and suggested a disease-modifying effect at the 1mg dose. However, this was not seen with the 2mg dose. Due to the conflicting results and the debated validity of the delayed-start trial design in proving neuroprotection, it remains unclear as to whether these results are clinically valid.
- *Selegiline: DATATOP* (Deprenyl And Tocopherol Antioxidative Therapy Of Parkinsonism)—a multicentre, placebo-controlled trial ($n = 800$) that investigated the effect of selegiline (10mg/day), tocopherol 2000iu/day (a compound with vitamin E activity), or placebo in early PD. Selegiline delayed the need for commencement of dopaminergic therapy, and tocopherol did not demonstrate any therapeutic benefit.

A meta-analysis of 17 RCTs (n = 3525) concluded that MAO-B inhibitors reduce disability, the need for levodopa (0.57, 0.48–0.67; p <0.00001), and the incidence of motor fluctuations (0.75, 0.59–0.95; p = 0.02), without substantial side effects or increased mortality (OR 1.13, 95% CI 0.94–1.34; p = 0.2).

The MDS review found selegiline to be efficacious as a monotherapy. There is insufficient evidence to support a neuroprotective effect of selegiline.

Dosing and monitoring

- *Rasagiline*: treatment is with 1mg od. Levodopa dose may be reduced based on symptom control.
- *Selegiline*: start treatment at 5mg in the morning. This dose can be increased to a maximum of 10mg/day, either as a single dose or bd, after 2–4 weeks (1.25mg of the dissolvable tablet is bioequivalent to 10mg standard tablet). Levodopa dose may subsequently be reduced based on symptom control.

Routine monitoring

- None.

Pharmacokinetics and interactions

Pharmacokinetics See Table A.23.

Interactions See Table A.24.

Table A.23 Pharmacokinetics of MAOIs

	Selegiline	Rasagiline
Main routes of administration	PO	PO
Oral bioavailability	~5%	36%
T_{max}	0.5–2h	1h
Protein binding	90%	88–94%
Metabolism	Hepatic, primarily via CYP2B6	Hepatic, primarily via CYP1A2
Pharmacologically active metabolites	Yes	No
Elimination half-life	10h	1–3h

PO, oral.

Table A.24 Interactions of MAOIs

Medications which alter MAO-B inhibitor plasma levels	Pharmacodynamic interactions
1. Selegiline **Levels increased:** contraceptives 2. Rasagiline: **Levels decreased:** CYP1A2 inducers, e.g. cyproterone **Levels increased:** CYP1A2 inhibitors, e.g. ciprofloxacin	**With sympathomimetics:** may enhance hypertensive effects **With antidepressants:** may increase the risk of serotonin syndrome. (see product literature for recommended washout periods) **With tramadol:** may increase the risk of seizures **With antihypertensives:** may increase the risk of orthostatic hypotension

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Non-ergot-based dopamine agonists

Non-ergot-based DAs have now superseded the ergot-derived agents due to their better side effect profiles. They are most commonly used in early PD, in order to minimize motor complications seen with levodopa use. They are also preferred to levodopa in the management of RLS, as there is a lower chance of augmentation. Pramipexole and ropinirole are available in oral formulations, while rotigotine is available as a transdermal patch, and apomorphine as an SC infusion/injection.

Uses

Licensed uses

In the UK/USA

- *PD*.
  1. *Apomorphine* is licensed for the treatment of 'on–off' phenomena in PD not adequately controlled by oral medication in individuals aged 18 years and older.
     Typically, SC injections into the lower abdomen or outer thigh are used if there are <10 sudden off periods per day. Continuous SC infusion is used if there are ≥10 sudden off periods in a day or painful end-of-dose dyskinesia/dystonia.
  2. *Pramipexole* is licensed for the treatment of PD as a monotherapy or as an adjunct to levodopa throughout the course of the disease in individuals aged 18 years and older.
  3. *Ropinirole* is licensed for the treatment of PD as a monotherapy or as an adjunct to levodopa throughout the course of the disease in individuals aged 18 years and older.
  4. *Rotigotine* is licensed for the treatment of PD as a monotherapy in early disease or as an adjunct to levodopa over the course of the disease when the effect of levodopa becomes less consistent in individuals aged 18 years and older.
- *RLS*.
  1. *Pramipexole* is also licensed for the treatment of moderate to severe RLS in individuals aged 18 years and older.
  2. *Ropinirole* (standard tablet) is also licensed for the treatment of moderate to severe primary RLS in individuals aged 18 years and older.
  3. *Rotigotine* is also licensed for the treatment of moderate to severe primary RLS in individuals aged 18 years and older.

Off-licence uses

- None.

Mechanism of action

The antiparkinsonian effects of the non-ergoline-derived DAs arise from action at primarily central post-synaptic D2 receptors within the striatum. This is also thought to be the mode of action when treating RLS. Due to action at presynaptic D2 receptors, which inhibit the release of dopamine, there may be an initial deterioration in PD symptoms. Apomorphine has affinity for D1 and D2 receptors, while the other agents act primarily on D2 and D3.

Toxicity and side effects

- *Common—cardiovascular*: orthostatic hypotension, peripheral oedema, and syncope. *Gastrointestinal*: constipation, nausea, and vomiting. *Neurological*: dizziness, dyskinesias, fatigue, hallucinations, headache, insomnia, sleep disorder, and somnolence (may be sudden onset).
- *Serious—cardiovascular*: AF, chest pain, long QT syndrome, and tachycardia. *Haematological*: haemolytic anaemia has been reported with apomorphine. *Musculoskeletal*: rhabdomyolysis (only pramipexole). *Psychiatric*: aggression, agitation, DAWS, ICDs, paranoia, and psychosis.

Contraindications

- *Absolute*: hypersensitivity to a drug or any of its excipients. Apomorphine should not be used in patients with respiratory depression, dementia, psychotic diseases, and hepatic insufficiency, in patients whose 'on' response to levodopa has significant dyskinesia/dystonia, or alongside 5HT3 antagonists (e.g. ondansetron), as this may lead to significant hypotension. The rotigotine patch should be removed prior to MRI and cardioversion, as it contains aluminium. Ropinirole should not be used if the creatinine clearance (CrCl) is <30mL/min without dialysis (no dose adjustment required in mild to moderate renal impairment). The ropinirole prolonged-release tablet should not be used in any degree of hepatic impairment, and the standard-release tablet should not be used in severe hepatic impairment.
- *Relative*: for apomorphine, reduce the test dose and starting dose to 1mg in moderate to severe renal impairment.

  Cardiovascular disease, patients at risk of long QT syndrome, and neuropsychiatric illness are relative contraindications for pramipexole, ropinirole, and rotigotine.

  Pramipexole dose should be lowered in renal dysfunction, as this is the primary route of elimination. CrCl 20–50mL/min: initiate at 0.088mg base (0.125mg salt) bd, and increase to a maximum daily dose of 1.57mg base (2.25mg salt). CrCl <20mL/min: initiate at 0.088mg base (0.125mg salt) od, and increase to maximum daily dose of 1.1mg base (1.5mg salt). Pramipexole dose does not need to be adjusted in hepatic impairment.

  Rotigotine does not require dose adjustment in renal impairment but should only be used with caution in patients with severe hepatic impairment.

Uses in special populations

- *Elderly*: no dose alteration is routinely required; however, extra caution should be taken when first starting treatment (particularly apomorphine), as the elderly are at increased risk of postural hypotension.
- *Pregnancy*: no safety data exist from human studies. No teratogenicity has been noted in animal studies, although some DAs have been shown to be embryotoxic. Use of these drugs should be avoided, unless the benefits outweigh risks.
- *Lactation*: excretion into breast milk is not known for most of these agents; DAs may reduce lactation; hence manufacturers advise against use by nursing mothers.

Efficacy

- *Apomorphine*: several double-blind studies have evaluated the efficacy of SC apomorphine in providing rescue from 'off' episodes in patients with advanced PD. *APO202*, a double-blind, placebo-controlled study, evaluated the efficacy of apomorphine ($n = 18$) administered, as needed, as rescue therapy from spontaneous 'off' episodes in patients with advanced PD who were experiencing >2h 'off' time per day, despite optimal oral therapy. ~95% of 'off' episodes per patient were successfully treated, compared with 23% with placebo ($p < 0.001$).
- *Pramipexole*: a 12-week randomized, double-blind, placebo-controlled trial of pramipexole in early PD ($n = 311$) found a significant reduction in UPDRS at all doses, compared to placebo, of 4.4–4.7 points, depending on the dose used ($p < 0.0001$ for each comparison to placebo). Quality of life, as measured by Parkinson's disease questionnaire-39 (PDQ-39), was significantly improved in the 0.75mg bd and 0.5mg tds groups ($p < 0.05$), but not in the 0.5mg bd group. Long-term efficacy and tolerability of pramipexole was confirmed in a 57-month open-label extension of a double-blind RCT ($n = 262$).
- *Ropinirole*: a double-blind RCT evaluated the effect of ropinirole (0.75–24mg/day), sumanirole (a highly selective D2 agonist not approved for medical use, 1–16mg/day), and placebo over 40 weeks in patients with PD ($n = 614$). There were significant improvements in UPDRS from baseline (−5.2), compared to worsening with placebo (0.38). The main adverse events were somnolence and nausea.
- *Rotigotine*: a randomized, double-blind, controlled trial compared the effect of rotigotine (8mg/day), ropinirole (24mg/day), and placebo on patients with early PD ($n = 561$). Rotigotine was significantly more effective than placebo, with a reduction of 52% vs 30% with placebo in UPDRS scores ($p < 0.0001$). Rotigotine was not inferior to ropinirole; however, the study was not sufficiently powered to differentiate which medication was more effective.

Dosing and monitoring

- *Apomorphine*.
  - *PD: SC injection*: the 'threshold dose' needs to be established before treatment can begin. Other PD medications should be firstly withheld to establish this dose. To prevent nausea and vomiting, patients should be pre-treated with domperidone 20mg tds for 3 days, and testing should be performed in a specialist clinic. Start treatment at 1mg, and assess response at 30min. Increase the dose by 1mg, and continue to assess the level of response and tolerability. The effective dose will result in >20% improvement in UPDRS score. The manufacturer advises that the total daily dose should not exceed 100mg and that individual bolus injections should not exceed 10mg. When the threshold dose is established, it can be administered SC at the first signs of an off period.
  Continuous SC infusion: start treatment at 1mg/h. Increase the dose by 0.5mg/h every 4h, up to a maximum of 4mg/h, depending on

clinical response. The infusion should be stopped overnight to prevent tolerance from developing. The infusion site should be changed 12-hourly. The dose of levodopa and other dopaminergic agents required may be reduced.

- *Pramipexole*.
  - *PD*: start treatment at 0.088mg base (0.125mg salt) tds. The dose can be increased after 1 week to 0.18mg base (0.25mg salt) tds, and then to 0.35mg base (0.5mg salt) tds after another week. The maximum daily dosage is 3.3mg base (4.5mg salt). Dose escalation should balance symptom improvement with the onset of side effects.
  - *RLS*: start treatment at 0.088mg base od, and increase, according to symptoms and tolerability, to a maximum dose of 0.54mg base od.
- *Ropinirole*.
  - *PD*: increase by 0.25mg tds each week to 1mg tds over 4 weeks. This is usually presented as a 'starter pack'. Following this, larger increases in dose can be made. A 'follow-on' pack is available which increases the daily dose from 1mg to 3mg tds over 4 weeks, as tolerated. Maximum dose 24mg/day. Prolonged-release tablets allow for od dosing. Start treatment at 2mg od for the first week; this can be increased every 2 weeks by 2mg, until adequate symptom control is reached. Maximum dose 24mg/day. Levodopa dose may be reduced when DAs are used as adjuncts.
  - *RLS*: start treatment at 0.25mg od prior to sleep. If tolerated, this can be increased at 0.5mg after 2 days, then to 1mg after a further 5 days, then by 0.5mg every week up to a usual maintenance dose of 2mg od. A maximum dose of 4mg od can be used, if required.
- *Rotigotine*.
  - *PD*: start treatment at 2mg/24h (advanced PD: 4mg/24h), and increase weekly by 2mg/24h. Usual treatment dose 6–16mg/24h.
  - *RLS*: start treatment at 1mg/24h. Increase weekly by 1mg/24h. The maximum recommended dose is 3mg/24h.

Monitoring

- Treatment withdrawal: gradual dose reduction should occur to minimize the risk of NMS and DAWS.
- With apomorphine: FBC, renal, hepatic, and cardiovascular function should be monitored at baseline and 6-monthly thereafter.

Pharmacokinetics and interactions

Pharmacokinetics See Table A.25.

Interactions See Table A.26.

Table A.25 Pharmacokinetics of non-ergot-based DAs

	Apomorphine	Pramipexole	Ropinirole	Rotigotine
Main routes of administration	SC	PO	PO	Patch
Oral bioavailability	100%	90–100%	50%	Variable
T_{max}	10min	2h	1–2h ER: 6–10h	15–18h
Protein binding	85–90%	15%	40%	90%
Metabolism	NA	Negligible (<10%)	Hepatic CYP1A2, CYP3A4	Hepatic CYP isoenzymes
Pharmacologically active metabolites	NA	No	No	No
Elimination half-life	40min	8.5h	6h	5–7h

ER, extended release; NA, information not available; PO, oral; SC, subcutaneous.

Table A.26 Interactions of non-ergot-based DAs

Medications which alter non-ergot-based DA plasma levels	Pharmacodynamic interactions
1. Pramipexole **Levels increased:** drugs which inhibit secretory transport at the renal tubules, e.g. cimetidine 2. Ropinirole **Levels decreased:** CYP1A2 inducers, e.g. cyproterone **Levels increased:** high-dose oestrogens and CYP1A2 inhibitors	**With antidopaminergic agents, e.g. antipsychotics:** can antagonize the effect of DAs **With antihypertensives:** increased risk of hypotension **Apomorphine, with agents known to prolong QTc, e.g. macrolide antibiotics:** may increase QTc interval

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Non-steroidal anti-inflammatory drugs

NSAIDs are central to the treatment of many headache disorders. Aspirin, or acetylsalicylic acid, was the first NSAID to be synthesized in the mid-nineteenth century. There are >20 NSAIDs available today. Those licensed for use in migraine include diclofenac, ibuprofen, and tolfenamic acid. Indometacin is also commonly used in headache disorders. It has a prominent role in specific headache disorders, including TACs. For aspirin see pp. 396–8.

Uses

Licensed uses

In the UK

- *Migraine*.
  1. *Diclofenac*: is licensed for the treatment of migraine in individuals aged 18 years and older.
  2. *Ibuprofen*: is licensed for the management of acute migraine in individuals aged 12 years and older.

In the USA

- *Migraine*.
  1. *Diclofenac*: is licensed for the treatment of migraine in individuals aged 18 years and older.
- *Analgesia*.
  1. *Ibuprofen*: is licensed for the management of mild to moderate pain in individuals aged 6 months and older.

In the UK/USA

1. *Indometacin* has no licensed neurological use.

Off-licence uses

1. *Diclofenac*: other headache disorders.
2. *Ibuprofen*: none.
3. *Indometacin*: can be used in the acute management of indometacin-responsive headaches, including HC, PHs, primary stabbing headache, and Valsalva-induced headache.

Mechanism of action

NSAIDs inhibit the cyclo-oxygenase (COX) enzymes COX-1 and COX-2. The COX enzymes convert arachidonic acid to prostanglandins and thromboxanes, both of which are the end-products of fatty acid metabolism and are involved in a number of biologically important processes, including gastric protection, inflammation, pain, fever, platelet aggregation, and vascular homeostasis. Inhibition of COX-2 is believed to be responsible for the anti-inflammatory, analgesic, and antipyretic properties of NSAIDs. COX-1 is found in almost all tissues and has a number of roles, including gastric protection. Inhibition of this enzyme is thought to result in the majority of use-limiting side effects of NSAIDs, including gastric ulceration. NSAIDs differ with respect to their differential activity at COX enzymes and their pharmacokinetics.

Toxicity and side effects: class effects

- *Common—dermatological*: maculopapular rash, urticaria. *Gastrointestinal*: diarrhoea, dyspepsia, nausea, vomiting. *Neurological*: dizziness, drowsiness, headache, tinnitus, vertigo.
- *Serious—cardiovascular*: MI, fluid retention resulting in new or worsening heart failure. *Dermatological*: Stevens–Johnson syndrome, toxic epidermal necrolysis. *Gastrointestinal*: peptic ulcer disease. *Haematological*: aplastic anaemia. *Neurological*: aseptic meningitis is sometimes seen, usually in patients with connective tissue disorders such as SLE. Cognitive impairment, convulsions, and stroke. *Renal*: interstitial nephritis, papillary necrosis, renal cell cancer. *Respiratory*: anaphylaxis, bronchospasm. *Psychiatric*: psychosis.

Contraindications

- *Absolute*: active gastrointestinal bleeding/ulceration, asthma if known to experience bronchospasm with NSAIDs, coagulopathy, hypersensitivity to aspirin or any other NSAID.
- *Relative*: inflammatory bowel disease can be worsened by NSAIDs. NSAIDs should be avoided in patients with pre-existing heart failure, ischaemic heart disease, and liver and renal failure.

Uses in special populations

- *Elderly*: NSAIDs should be used with caution in the elderly, as they are more likely to have renal impairment and cardiovascular disease. Polypharmacy is also commoner in the elderly population, and NSAIDs have numerous drug interactions. NSAIDs should only be used if absolutely necessary and in the smallest effective dose for the shortest time possible.
- *Pregnancy*: NSAIDs should be avoided in the last trimester, due to a risk of early closure of the ductus arteriosus, oligohydramnios, renal dysfunction, and, particularly in premature infants, intracranial haemorrhage. With regard to the rest of pregnancy, NSAIDs should be avoided, unless benefits outweigh risks.
- *Lactation*: NSAIDs are present in small amounts in breast milk but are not believed to pose a risk to the neonate. It should, however, be used with caution in lactating mothers.

Efficacy

1. *Diclofenac—migraine*: a Cochrane review looking at diclofenac potassium 50mg vs placebo in the acute management of migraine found that the NNT for patients to be pain-free at 2h was 6.2, and to be pain-free at 24h 9.5. There was no difference between diclofenac 50mg and placebo for adverse events. In about half of those treated (55%), there was a significant reduction in pain at 2h from moderate/severe to mild, while 22% of patients had no pain at 2h. The review concluded that diclofenac potassium 50mg was a suitable oral treatment for acute migraine attacks.
2. *Ibuprofen—migraine*: a Cochrane review of ibuprofen in the management of acute migraine found that a single 400mg dose of ibuprofen significantly reduced headache from moderate/severe to no headache at 2h in 26% of patients, compared with 12% for placebo.

The NNT was 7.2. Twenty per cent of patients were headache-free at 2h with ibuprofen 200mg (NNT 9.7). The 400mg dose was more effective than 200mg at reducing headache severity ($p = 0.0002$). Adverse effects were minimal, and there was no significant difference between placebo and ibuprofen. In a meta-analysis of ibuprofen in acute migraine, the 400mg dose was found to significantly reduce photophobia by 30% ($p < 0.01$) and phonophobia by 49% ($p < 0.0001$), compared with placebo.

3. *Indometacin*: there are no RCTs assessing the use of indometacin in headache syndromes. *PH*: a retrospective case note study looking at indometacin use in 74 patients with chronic PH found that 30 patients had a reliable response to indometacin therapy, while the rest either had inconsistent responses or data were unavailable. Of the 30 who responded to indometacin, 24 responded completely.

Dosing and monitoring

1. *Diclofenac*: 50mg of diclofenac should be given at the onset of headache, and, if needed, a repeat dose can be given 2h later.
2. *Ibuprofen*: a single dose of 200mg or 400mg should be taken as soon as possible after the start of migraine.
3. *Indometacin*: start treatment at 75mg daily in divided doses, usually 25mg TDS. If there is no response or only a partial response after 48–72h, then the dose can be increased to a total of 150mg daily, and then to a further 225mg/day if no response after another 48–72 hour period. The drug is typically trialled for ~2 weeks at the highest tolerated dose before absence of a beneficial response is considered a treatment failure. A response is usually seen within 48–72h of initiation.

Routine monitoring

1. *Diclofenac*: routine monitoring is not required for diclofenac in the acute management of migraine.
2. *Ibuprofen*: only advised in the acute management of migraine and should not be used regularly for >10 days due to the risk of adverse effects, particularly gastrointestinal ulceration.
3. *Indometacin*: the regular use of indometacin is associated with severe toxicity, with 10% of patients experiencing a serious adverse effect. Patients should be monitored for hepatic, renal, gastrointestinal, and haematological toxic effects. In particular, patients are at risk of aplastic anaemia and agranulocytosis, and should be monitored for this with regular FBCs.

Pharmacokinetics and interactions

Pharmacokinetics

NSAIDs are absorbed fully, and have little first-pass metabolism and small volumes of distribution. Most are highly bound to albumin. They differ in their half-lives: diclofenac (~1h), ibuprofen (~2h), and indometacin (~4.5h). NSAIDs are eliminated by the kidney, after glucuronidation and/or transformation by the liver cytochrome P450 system. Very little of the drug is excreted unchanged (<5%).

Interactions See Table A.27.

Table A.27 Interactions of NSAIDs

Medications which alter NSAID plasma levels	Medications whose plasma levels are altered by NSAIDs	Pharmacodynamic interactions
Levels increased: diclofenac: ciclosporin and imatinib; ibuprofen: azole antifungals; indometacin: diflunisal and probenecid	**Levels increased:** baclofen, digoxin, warfarin, lithium, and methotrexate	**With ACE inhibitors/angiotensin receptor blockers, calcineurin inhibitors, diuretics:** renal toxicity **With antidepressants (SSRIs and venlafaxine), anticoagulants, antiplatelets, and corticosteroids:** increased risk of bleeding **With antihypertensives:** NSAIDs antagonize hypotensive effect **With potassium-sparing diuretics:** increased risk of hyperkalaemia **With quinolones:** increased risk of seizures **With sulfonylureas:** concomitant use can induce hypoglycaemia

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Opioids

Opioids are among some of the oldest known drugs. The medical and recreational use of opium dates back to at least 4000 BC. Morphine and other opioid drugs, both naturally occurring opiates and synthetic opioids, act by binding to the opiate receptors μ, κ, and δ. Morphine predominantly produces its analgesic and euphoric effects through the μ-opioid receptor.

In neuropathic pain, the most studied opioid drugs are fentanyl, morphine, oxycodone, and tramadol. Although opioid drugs generally provide very good analgesia, their long-term use is restricted by their side effect profile and the risks of substance misuse and tolerance.

Uses

Licensed uses

- Pain.

In the UK/USA

1. *Fentanyl*.

Fentanyl is licensed for malignant and non-malignant chronic intractable pain in individuals above the age of 2 years. IV preparations are only licensed for use in individuals above the age of 12 years. Buccal preparations are licensed for chronic cancer pain in opioid-tolerant patients above the age of 16.

2. *Morphine*.

In the UK, PO morphine is licensed for the treatment of moderate to severe pain in individuals above the age of 1 year. Note that Oramorph® solution and MXL® capsules are not licensed for use in children under 1 year; Filnarine® SR and Sevredol® tablets are not licensed for use in children under 3 years, and MST Continus® preparations are only licensed in children to treat cancer pain. In the USA, oral morphine is licensed for the treatment of moderate to severe pain in adults.

3. *Oxycodone*.

Oxycodone is licensed for moderate to severe pain in individuals above 18 years of age.

4. *Tramadol*.

Tramadol is licensed for moderate to severe pain in individuals over the age of 12 years (UK)/16 years (USA).

Mechanism of action

Morphine and oxycodone are the most studied opioids in the context of neuropathic pain. Both are μ-opioid receptor agonists, although oxycodone also antagonizes κ-opioid receptors. Fentanyl is a very potent μ-opioid receptor agonist. The overall effect of opioid drugs is to reduce spinal nociceptive transmission.

Toxicity and side effects: class effects

- *Common—cardiovascular*: bradycardia, oedema, palpitations, postural hypotension, tachycardia. *Dermatological*: flushing, pruritus, rash, sweating, urticaria. *Gastrointestinal*: biliary spasm, constipation, dry mouth, nausea, vomiting. *Neurological*: confusion, dizziness, drowsiness, headache, vertigo. *Ophthalmological*: miosis, visual disturbance. *Psychiatric*: dependence, dysphoria, euphoria, hallucinations, mood changes, sleep disturbances. *Respiratory*: bronchospasm. *Urological*: difficulty with micturition, ureteric spasm, urinary retention.

Note: With larger doses, muscle rigidity and hypotension occur. Tolerance and substance abuse preclude long-term usage.

- *Serious—gastrointestinal*: paralytic ileus. *Neurological*: seizures. *Respiratory*: respiratory depression.

Contraindications

- *Absolute*: any patients with acute respiratory depression, paralytic ileus, raised ICP, and head injuries (affect assessment of pupillary responses); comatose patients.
- *Relative*: reduce dose in hepatic impairment (risk of precipitating encephalopathy); reduce dose in renal impairment (increased and prolonged effect, and increased cerebral sensitivity), impaired consciousness, COPD, acute asthma, hypotension, shock, MG, prostatic hypertrophy, obstructive or inflammatory bowel disorders, diseases of the biliary tract, and convulsive disorders. Reduce dose in the elderly, debilitated, hypothyroidism, and adrenocortical insufficiency. Caution is recommended while prescribing opiates to patients with a history of drug dependence. Tramadol can lower the seizure threshold and should be avoided in epilepsy.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function, and benefit from halving the adult dosing regimen.
- *Pregnancy*: opiates depress neonatal respiration; withdrawal effects in neonates of dependent mothers. Use with caution in pregnancy.
- *Lactation*: therapeutic doses of morphine, tramadol, and fentanyl are unlikely to affect the breastfeeding infant; however, there is the small potential of withdrawal symptoms in infants of dependent mothers. Use if benefits outweigh risks. Oxycodone is present in breast milk. Infant sedation occurs commonly with maternal use, and there is a risk of infant CNS depression and death. Neonates have a reduced clearance of oxycodone. Only use if benefits outweigh risk, and there is no alternative analgesic. A maximum maternal dose of 30mg/day is recommended, and the infant should be monitored for drowsiness, adequate weight gain, and developmental milestones.

Efficacy

A Cochrane review evaluated the efficacy of opioid drugs in relieving neuropathic pain. Thirty-one trials were identified, but the majority were short-term, and heterogeneity precluded cross-study quantitative analysis. However, 14 longer-term trials (lasting up to 12 weeks), involving 845 patients, demonstrated efficacy for opioids with various types of neuropathic pain. A meta-analysis revealed that, of the patients taking an opioid drug, 57% received >33% pain relief, compared to 34% of those receiving the placebo, with an NNT of 4.0 (95% CI 3.0–5.6). A recent systematic review demonstrated that both IV and PO morphine were effective in the treatment of phantom limb pain both in the short and long term. Opioid drugs are viewed as non-superior to TCAs by both the EFNS and NICE. It is recommended that they are used second- or third-line and only for a short duration when antidepressants and anticonvulsants have failed.

Tramadol: a systematic review identified five placebo-controlled trials, which all showed tramadol to be more effective than placebo in treating neuropathic pain. A meta-analysis of these trials (303 total participants) showed that tramadol was more effective than placebo in achieving >50% pain relief, with an NNT of 3.8 (95% CI 2.8–6.3). Tramadol is recommended by the EFNS as a second- or third-line analgesic for the long-term treatment of neuropathic pain, but it can be used as a first-line option for acute exacerbations of painful diabetic neuropathy.

Dosing and monitoring

Consideration of the following factors must be taken into account when starting a patient on an opioid drug: total daily dose, potency, patient's degree of opioid tolerance, patient co-morbidities, concurrent medications, and type and severity of pain.

For converting between opioids, see Table A.28.

Dosing

1. *Fentanyl*—for fentanyl transdermal patches: start treatment at 12–25 micrograms/h patch every 72h. Base dose increments on the daily dose of supplementary opioid analgesics. Maximal analgesia will be achieved after 24h, so consider using a short-acting opioid as breakthrough analgesia until this time.
2. *Morphine*—starting dose: po 5–10mg every 4h, as required. The parenteral dose is approximately three times as strong as the oral dose. Initially, titrate with short-acting formulations; when an average daily dose is established, convert to longer-acting opioids or transdermal applications. To convert to extended-release preparations, administer 50% of the patient's 24h requirement bd or one-third of the daily morphine dosage tds.
3. *Oxycodone*—starting dose: for immediate-release preparations, 2.5–5mg po every 4–6h. Trial 4–6 weeks. Increase the dose slowly, as required. Doses >30mg daily are rarely needed. Maximum dose 400mg/24h, but some patients will require higher doses. Patients on high long-term doses of oxycodone should be converted to a sustained-release preparation. Halve the oral dose if administering parenterally.
4. *Tramadol*—for the treatment of neuropathic pain, start treatment at 25mg every morning. Uptitrate by 25mg every 3 days, in separate doses, to reach a qds regimen (25mg qds). Then increase the total daily dose by 50mg every 3 days. Trial for 4 weeks. Note, if a more rapid

Table A.28 Opioid drug dose conversions

Fentanyl: transdermal	Morphine: oral	Oxycodone: oral	Tramadol: oral
12.5 micrograms/h	30–59mg/24hrs	15–29.5mg/24hrs	150–300mg/24hrs
25 micrograms/h	60–134mg/24hrs	30–67mg/24hrs	301–600mg/24hrs
50 micrograms/h	135–224mg/24hrs	67.5–112mg/24hrs	NA
75 micrograms/h	225–314mg/24hrs	112.5–157mg/24hrs	NA
100 micrograms/h	315–404mg/24hrs	157.5–202mg/24hrs	NA

NA, information not available.

onset of analgesic effect is required, patients can be started on 50–100mg tramadol every 4–6h. Maximum dose 400mg daily. In patients with chronic pain, sustained-release preparations can be used, with an initial dose of 100mg daily, increased every 5 days by 100mg to a maximum dose of 300mg daily.

Routine monitoring None required.

Pharmacokinetics and interactions

Pharmacokinetics See Table A.29.

Table A.29 Pharmacokinetics of opioids

	Fentanyl	Morphine	Oxycodone	Tramadol
Main routes of administration	BC/IN/IV/SC/SL/TD	IV/IM/SC/PO	IV/IM/SC/PO	PO (IV/IM)
Oral bioavailability	50–90% for BC/SL/TD routes	20–40%	95–100%	75–95%
T_{max}	BC: 35–45min SL: 45min to 1.5h TD: 20–72h	SC/IM: 20min PO: 30–90min	PO: 1h For modified-release preparations: PO, 3h	PO: 10–12h
Protein binding	80–85%	30–35%	45%	20%
Time to steady state	IV: 18–24h TD: 144h	24h	18–24h	4 days
Pharmacologically active metabolites	No	Yes, strong activity	Yes, strong activity	Yes, strong activity
Elimination half-life	IV: 219min BC: 2–11h SL: 7–15h TD: 13–22h	2–4h	3–4h	6–10h
Metabolism	CYP3A4	UDP-glucuronosyltransferase-2B7	CYP2D6, CYP3A4	CYP2B6, CYP2D6, CYP3A4
Excretion	As metabolites: urine >90%, faecal 1% Unchanged: urine 7%	As metabolites: urine 80%, faeces 10% Unchanged: urine 10%	As metabolites: urine 65% Unchanged: urine 20%	As metabolites: urine 60% Unchanged: urine 30%

BC, buccal; IN, intranasal; IV, intravenous; PO, oral; PR, per rectum; SC, subcutaneous; SL, sublingual; TD, transdermal.

Interactions See Table A.30.

Table A.30 Interactions of opioids

Medications which alter opioid drug plasma levels	Medications whose plasma levels are altered by opioid drugs	Pharmacodynamic interactions
Levels decreased: CYP450 enzyme inducers, e.g. carbamazepine, phenytoin **Levels increased:** fentanyl: CYP450 enzyme inhibitors, e.g. cimetidine, macrolide antibiotics, ritonavir, and triazoles; oxycodone: voriconazole	**Levels decreased:** none **Levels increased:** fentanyl: etomidate; morphine: esmolol and gabapentin	**With alcohol, antihistamines, antipsychotics, baclofen, and benzodiazepines:** enhanced sedative and often hypotensive effects **With coumarins:** tramadol enhances the anticoagulant effect **With MAOIs, SNRIs, and SSRIs:** tramadol enhances serotonergic effects **With domperidone and metoclopramide:** antagonism of gastric emptying

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Phenytoin and fosphenytoin

Phenytoin is a widely used broad-spectrum AED. Its main disadvantages are:
1. non-linear pharmacokinetics requiring regular monitoring of plasma levels;
2. high levels of pharmacokinetic interactions;
3. IV injections are associated with local toxic effects, due to the fact that phenytoin is water-insoluble and hence administered with alcohol and propylene glycol at a pH of 14;
4. long-term use is associated with dysmorphism, hirsutism, and hypertrichosis.

Fosphenytoin is a phenytoin prodrug, and hence the majority of its side effects and interactions are identical to phenytoin. Its main advantage over phenytoin is that it is water-soluble, and the concentrate for injection is at a physiological pH. This avoids injection site toxicity of phenytoin and allows it to be given IM if IV administration is not an option (although IM injection should not be used in the treatment of status, as T_{max} can take >24h by this route of administration). It can be administered faster than phenytoin when given IV. It is only available by injection; hence its main use is in status epilepticus. Its main clinical effects are attributable to phenytoin, with which it shares many pharmacokinetic characteristics and side effects.

Uses

Licensed uses

In the UK/USA

1. *Fosphenytoin*.
   - *Epilepsy*: fosphenytoin is licensed for the treatment of tonic–clonic status epilepticus, for the prevention and treatment of seizures during or following neurosurgery (UK: and/or head trauma), and as a substitute for oral phenytoin if oral administration is not possible in individuals of all ages.
2. *Phenytoin*.
   - *Epilepsy*: phenytoin is licensed for the treatment of tonic–clonic seizures, focal-onset seizures with or without secondary generalization, and seizures occurring during or following neurosurgery (UK: and/or head injury) as a monotherapy or as an adjunct in individuals of all ages. Phenytoin as an injection or infusion is licensed for the treatment of tonic–clonic status epilepticus in individuals of all ages.

Mechanism of action

The mechanism of action of phenytoin has not been fully established. It is thought that its main antiepileptic activity is via use-dependent blockade of voltage-sensitive sodium channels. It also regulates calmodulin and secondary messenger systems, enhances post-synaptic GABA-mediated inhibition, and inhibits the action of calcium channels presynaptically in order to block the release of neurotransmitters. Fosphenytoin has no known pharmacological activity prior to conversion to phenytoin.

Toxicity and side effects

- *Common—dermatological*: rash can occur, and treatment should be stopped and only restarted if settling and mild in nature. If it reoccurs, then stop treatment permanently. Acne, hirsutism, hypertrichosis, and dysmorphism in the form of coarse facial features are common with long-term treatment. *Gastrointestinal*: anorexia, constipation, gingival hypertrophy, nausea, and vomiting. *Neurological*: headache, paraesthesiae, sedation, and tremor are common.

  In addition, the following side effects have been reported with fosphenytoin use.

  Common—gastrointestinal: dry mouth and taste disturbance. *Neurological*: dysarthria, tinnitus, visual disturbances, and weakness. *Psychiatric*: euphoria. *Dermatological*: bruising and pruritus.

- *Serious—cardiovascular*: IV injection can cause hypotension, arrhythmias, and cardiovascular collapse, particularly if given too rapidly. BP and continuous cardiac monitoring are mandatory during IV administration. *Dermatological*: Stevens–Johnson syndrome and toxic epidermal necrolysis have rarely been reported. Purple glove syndrome: a purple discoloration and oedematous change to the skin, followed by subsequent necrosis. It is caused by phenytoin extravasation around the cannula site. There are no reports of purple glove syndrome with fosphenytoin use. *Gastrointestinal*: rarely, a toxic hepatitis can occur. *Haematological*: rarely aplastic anaemia, lymphoma, and pancytopenia have been reported. *Immunological*: PAN and SLE have rarely been reported. *Neurological*: rarely, irreversible cerebellar dysfunction can occur. *Psychiatric*: psychosis and suicidal ideation have been reported. *Renal*: interstitial nephritis is rare. *Respiratory*: pneumonitis and rapid IV administration can cause respiratory arrest.

Of note, less commonly, anaemia (often related to folic acid deficiency), osteomalacia, and weight gain can occur with long-term use.

Contraindications

- *Absolute*: hypersensitivity to phenytoin or its excipients.
- *Relative*: phenytoin is ineffective in the treatment of absence seizures, myoclonic jerks, childhood epileptic encephalopathy, and the progressive myoclonic epilepsies. Phenytoin undergoes extensive hepatic metabolism and is renally excreted; hence the dose should be lowered in hepatic and renal impairment. Monitoring of free non-protein-bound phenytoin plasma concentrations should guide dosing in these circumstances.

  There is a cross-over with the rash associated with carbamazepine treatment (up to 50% of patients who had a skin rash with carbamazepine also developed one with phenytoin in small studies); hence phenytoin should be used with caution in individuals with a history of carbamazepine-induced rash.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function and benefit from lower dosing regimens. Co-prescription of other medications is also more likely in the elderly, and hence the probability of pharmacokinetic interactions is high.

- *Pregnancy*: There is demonstrable evidence of teratogenic risk to the human fetus. Phenytoin impairs endogenous vitamin K synthesis and hence increases the risk of haemorrhagic disease of the newborn. A prophylactic injection of vitamin K should be given. In addition, free phenytoin levels can reduce by 30–80% during pregnancy; hence doses may need to be increased. Use in patients during pregnancy involves weighing up the potential benefits and side effects (see Antiepileptic drugs in young women, pp. 37–9).
- *Lactation*: it is not known if fosphenytoin is present in human breast milk, but phenytoin is. Plasma levels are <10% of those of the mothers. If used, infants should be monitored for potential side effects such as sedation and irritability. The infant should be switched to an alternative feeding regimen if these are identified.

Efficacy

1. *Fosphenytoin*: minimal evidence exists that looks specifically at fosphenytoin efficacy. One open-label study looked at the time to seizure cessation in patients with status epilepticus and found no significant difference between those given phenytoin or fosphenytoin. The maximal rate of fosphenytoin infusion is three times faster than that of phenytoin. However this does not necessarily correlate with faster attainment of effective plasma phenytoin levels, which may be delayed as fosphenytoin needs to be converted by phosphatases to phenytoin.
2. *Phenytoin*: there are relatively little data from high-quality studies regarding efficacy of phenytoin, but to date no AED has been shown to be superior. Current trials are investigating whether IV valproate or levetiracetam may be safer to use in status epilepticus. A 2001 Cochrane review demonstrated that phenytoin was effective at preventing post-traumatic seizures arising before 1 week but not after 1 week following brain injury. Hence administration of short-term phenytoin following moderate to severe head injuries to prevent early post-traumatic seizures is common. There is as yet little evidence to recommend routine prophylaxis of patients with cerebral space-occupying lesions or cerebral haemorrhage, thrombosis, and stroke. See Status epilepticus, pp. 41–5, and seizures in neuro-oncology under Management of complications, pp. 195–6 for discussion of the evidence in these scenarios.

Dosing and monitoring

Routine monitoring

Hepatic and renal function should be assessed prior to initiating treatment and yearly thereafter. Measure folate and vitamin D levels on a regular basis.

Therapeutic drug monitoring Both AEDs should be monitored using phenytoin plasma levels: Optimum seizure control when used in monotherapy occurs at plasma concentrations of 10–20mg/L. Trough samples should be taken. When phenytoin is used as maintenance therapy outside of status epilepticus, take the sample when steady state is reached at 1–3 weeks post-dose adjustment.

In settings where protein binding is affected, e.g. concomitant administration of phenylbutazone, salicylates, tolbutamide, and valproate, or when albumin concentration is altered, dosing is best guided through measurement of free non-protein-bound plasma concentrations.

Dosing

1. *Fosphenytoin*: doses are expressed as phenytoin sodium equivalent (PE). Fosphenytoin sodium 1.5mg = phenytoin sodium 1mg. IM injection should not be used in status epilepticus.
   - *For the treatment of status epilepticus*—age >18 years: start treatment with a bolus dose by IV infusion of 20mg (PE)/kg at a rate of 100–150mg (PE)/min. Then give 4–5mg (PE)/kg daily, divided into 1–2 doses. Administer the maintenance doses at a rate of 50–100mg (PE)/min. Then adjust dosing according to clinical response and plasma phenytoin levels. BP, heart rate, and respiratory function monitoring are a requirement of IV administration.
   - *For prophylaxis or treatment of seizures associated with neurosurgery or head injury*—age >18 years: start treatment with a bolus dose by IM injection or IV infusion (at a rate of 50–100mg (PE)/min) of 10–15mg (PE)/kg. Then give 4–5mg (PE)/kg in total daily, divided into 1–2 doses, by IM injection or IV infusion (at a rate of 50–100mg (PE)/min). Then adjust dosing according to clinical response and plasma phenytoin levels.
   - *For use as a substitute to oral phenytoin*—age >18 years: use the same dose and frequency as oral phenytoin by IM injection or IV infusion (at a rate of 50–100mg (PE)/min).
2. *Phenytoin*.
   - *For the treatment of all forms of epilepsy, except absence seizures*, age >18 years: start treatment at 3–4mg/kg/day or 150–300mg/day in 1–2 divided doses. If given as a single dose, this should be given at night. The dose should be increased gradually, with plasma phenytoin monitoring, to a usual maintenance dose of 200–500mg daily. Dosage changes should not occur faster than at 1-week intervals and should be ideally increased at 3- to 4-week intervals. There is no documented difference in the bioavailability of tablets vs capsules. Oral doses should be taken with or after food.
   - *For the treatment of status epilepticus*: a loading dose of 20mg/kg (maximum of 2g) is used and given by IV injection or infusion at a rate <1mg/kg/min. Then maintenance doses of 100mg every 6–8h can be given PO or parenterally, and adjusted according to phenytoin concentration. BP and cardiac monitoring are a requirement of IV administration. A wide-bore cannula should be used with a large flush pre- and post-dose to minimize consequences of extravasation.

Pharmacokinetics and interactions

Pharmacokinetics

- *Fosphenytoin*: the bioavailability and T_{max} of fosphenytoin by the IM route is 100% and 0.5h, respectively. Fosphenytoin undergoes hydrolysis to form phenytoin by phosphatase enzymes mostly present in the liver and red blood cells. The half-life for fosphenytoin conversion to phenytoin

is 8–15min. T_{max} for phenytoin following administration of fosphenytoin is 0.5–1h by the IV route, and 1.5–4h by the IM route; Phenytoin steady state is reached in 6–21 days. The rest of pharmacokinetics of fosphenytoin are as per phenytoin.

- *Phenytoin*: different formulations have slightly different T_{max} and bioavailability values. The oral bioavailability is on average >80%. T_{max} varies between 1h and 12h. Steady state is reached in 1–3 weeks. Ninety per cent of phenytoin is protein-bound, predominantly to albumin. Between 75% and 100% of phenytoin is metabolized hepatically. Metabolites are inactive. The major metabolite is 5-(*p*-hydroxyphenyl)-5-phenylhydantoin, the majority of which is subsequently glucuronidated and eliminated via the renal system. Hydroxylation is mainly mediated by CYP2C9 and CYP2C19, which, alongside CYP1A2 and CYP3A4 isoenzymes, undergo autoinduction. This may necessitate an increase in dosage when steady state is reached. The phenytoin half-life increases at higher doses and in the absence of enzyme-inducing AEDs. The half-life averages 22h. The majority of metabolites of phenytoin are eliminated by the kidneys; <5% is eliminated as unchanged drug.

Interactions

See Table A.31. As a result of the magnitude of the interaction between diazoxide and phenytoin, whereby phenytoin plasma levels are decreased to almost non-detectable values, this drug combination can be considered contraindicated.

Table A.31 Interactions of phenytoin and fosphenytoin

Medications which alter phenytoin plasma levels	Medications whose plasma levels are altered by phenytoin
Levels decreased: CYP3A4, CYP2C9, CYP2C19, and CYP1A2 inducers, e.g. rifampicin and St John's wort	**Levels decreased:** CYP3A4, CYP2C9, CYP2C19, and CYP1A2 substrates, e.g. albendazole, amiodarone, and lamotrigine
Levels increased: CYP3A4, CYP2C9, CYP2C19, and CYP1A2 inhibitors, e.g. cimetidine, indinavir, and voriconazole	**Levels increased:** chloramphenicol, clobazam (metabolite), and phenobarbital

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Selective serotonin and noradrenaline reuptake inhibitors

SNRIs are a group of drugs most commonly used in the management of mood disorders. However, several of the SNRIs have also been demonstrated to have neurological applications. Three SNRIs (duloxetine, milnacipran, and venlafaxine) have been found to be effective in treating various forms of neuropathic pain. In addition, venlafaxine is used in the management of narcolepsy.

These drugs are generally very specific, only acting to increase the synaptic levels of 5-hydroxytryptamine (5HT) and noradrenaline (NA), with virtually no inhibition of monoamine oxidase. Duloxetine and venlafaxine are more potent inhibitors of serotonin uptake than NA, while milnacipran has a 3-fold higher inhibition of NA reuptake, compared to serotonin.

Uses

Licensed uses

In the UK/USA

1. *Duloxetine: neuropathic pain*—duloxetine is licensed for pain relief in diabetic neuropathy in adults.
2. *Milnacipran: fibromyalgia*—milnacipran is licensed for the treatment of fibromyalgia in individuals aged 18 years and older; it is not licensed for use in the UK.
3. *Venlafaxine*: venlafaxine is licensed for treatment of mood disorders in the UK and USA. There is no licensed neurological use in either country.

Off-licence uses

Venlafaxine is used off-licence for the treatment of narcolepsy and neuropathic pain.

Mechanism of action

- *Narcolepsy*: the mechanism of action of venlafaxine in the management of narcolepsy is unclear. Venlafaxine and other antidepressants may work through their combined noradrenergic and serotonergic activity. This may inhibit REM-on neurons in the brainstem, preventing spontaneous attacks of REM sleep.
- *Neuropathic pain*: SNRIs block 5HT and NA reuptake transporters, achieving analgesia in a similar fashion to TCAs. They have a narrower spectrum of activity than TCAs, which minimizes the extent of their side effect profile.

Toxicity and side effects

- *Common—cardiovascular*: hypertension, palpitations. *Dermatological*: flushing. *Gastrointestinal*: appetite change, constipation, dry mouth, nausea, vomiting, and weight change. *Neurological*: dizziness, headache, tremor. *Psychiatric*: abnormal dreams, insomnia.
- *Serious—cardiovascular*: hypertensive crisis. *Dermatological*: Stevens–Johnson syndrome. Duloxetine has been reported to cause anaphylaxis and angio-oedema. *Metabolic*: rhabdomyolysis. *Neurological*: seizures. *Ophthalmological*: angle-closure glaucoma. *Psychiatric*: suicidal behaviour.

With venlafaxine: additional side effects to be aware of include:
- *serious—cardiovascular*: QT prolongation. *Gastrointestinal*: pancreatitis. *Psychiatric*: NMS.

NB. Withdraw gradually. Symptoms of withdrawal include anxiety, dizziness, headache, nausea, paraesthesiae, sleep disturbances, tremor, and vomiting. In patients treated with venlafaxine for narcolepsy, abrupt cessation of venlafaxine has been associated with status cataplecticus, i.e. recurrent attacks of cataplexy with little or no refractory period.

Contraindications

All SNRIs.
- *Absolute*: concomitant use of MAOIs.
- *Relative*: angle-closure glaucoma, bleeding disorders, cardiac disease, elderly, mania, seizures, and uncontrolled hypertension.

In addition:
1. *Duloxetine*.
   - *Absolute*: hepatic impairment and renal impairment eGFR <30mL/min/1.73m^2.
2. *Milnacipran*.
   - *Relative*: renal impairment eGFR <30mL/min/1.73m^2; reduce the dose by 50%. No dose adjustment is neccessary in hepatic failure.
3. *Venlafaxine*.
   - *Absolute*: eGFR <10mL/min/1.73m^2.
   - *Relative*: eGFR 10–30mL/min/1.73m^2 (halve the dose) and hepatic impairment.

Uses in special populations

- *Elderly*: no dose adjustment is required in the elderly, although care with increasing doses is recommended.
- *Pregnancy*: there are no controlled data for use of SNRIs in pregnancy. There have been individual reports of increased neonatal complications, including feeding difficulties, irritability, and respiratory and neurological complications such as hyperreflexia, hypo-/hypertonia, and seizures. It is advised that the SNRIs should only be given in pregnancy, particularly in the third trimester, if the benefit outweighs the risk.
- *Lactation*:
  1. duloxetine is present in breast milk, although the effects on the developing infant are unknown. There is a small risk of neonatal withdrawal syndrome with duloxetine. Mothers are advised to avoid breastfeeding while on treatment;
  2. milnacipran: there are no studies available reporting the safety of milnacipran in breastfeeding. Manufacturer advises to avoid;
  3. venlafaxine and its metabolite *O*-desmethylvenlafaxine are both present in breast milk. No proven reports of side effects to date. Both the American Academy of Pediatricians and the National Institute of Health in the UK consider venlafaxine safe for breastfeeding.

Efficacy

1. *Duloxetine*: there is very good evidence from three high-quality systematic reviews. The most recent review identified 18 trials, including 6407 participants in total, 2728 patients with diabetic neuropathy and 2249 with fibromyalgia. For a >50% reduction in pain over a 12-week period in diabetic neuropathy, the NNT was 5 (95% CI 4–7), and in fibromyalgia it was 8 (95% CI 4–21). One small high-quality trial found no effect from duloxetine in treating central neuropathic pain.
2. *Milnacipran*: a recent systematic review identified five RCTs, with a total of 4138 participants, comparing milnacipran to placebo for pain relief in fibromyalgia. Doses of 100mg and 200mg provided >30% reduction in pain to 40% of those treated, compared to 30% of participants in the placebo arm. The NNT was 8.6 (95% CI 6.3–14). Milnacipran has not been studied in other forms of neuropathic pain.
3. *Venlafaxine*.
   - *Narcolepsy*: the evidence for venlafaxine in the management of narcolepsy comes purely from case study evidence and expert consensus statements. In case studies, symptoms of cataplexy, excessive daytime sleepiness, and hypnagogic hallucinations improved with the use of venlafaxine in the majority of subjects.
   - *Neuropathic pain*: a systematic review identified six studies investigating the effectiveness of venlafaxine in treating neuropathic pain. Three studies showed venlafaxine to be superior to placebo in significantly reducing global pain relief measurements, with an NNT of 3.1 (95% CI 2.2–5.1). These studies included patients with post-mastectomy pain, painful polyneuropathy, and experimentally induced pain. Three other studies only reported mean data. Venlafaxine has not been adequately studied in other forms of neuropathic pain, including painful diabetic neuropathy, post-herpetic neuralgia, and central pain.

Dosing and monitoring

Dosing

1. *Duloxetine*: start treatment at 30mg. Increase to 60mg od after 1 week. Maximum dose 120mg daily.
2. *Milnacipran*: start on day 1 with a single 12.5mg dose; on days 2–3, administer 12.5mg bd; on days 4–7, administer 25mg bd; after day 7, administer 50mg bd. Based on patient response, the dosage may be increased to 100mg bd.
3. *Venlafaxine*: starting dose: 37.5mg od. Increase the dose by 37.5–75mg each week, as tolerated. Usual maintenance dose is 75–225mg/day for neuropathic pain. In narcolepsy, maintenance doses of 150–375mg have been used in case studies.

Routine monitoring None routinely required for duloxetine and milnacipran. Venlafaxine was found to cause a dose-related increase in BP, particularly with doses >200mg. Controlling pre-existing hypertension before starting venlafaxine and routine BP monitoring thereafter is recommended.

Pharmacokinetics and interactions

Pharmacokinetics See Table A.32.

Interactions See Table A.33.

Table A.32 Pharmacokinetics of SNRIs

	Duloxetine	Milnacipran	Venlafaxine
Main routes of administration	PO	PO	PO
Oral bioavailability	50%	85%	42%
T_{max}	6h	2–4h	5.5h
Protein binding	95%	13%	30%
Time to steady state	3 days	2 days	3 days
Pharmacologically active metabolites	No	Yes, strong	Yes, strong
Elimination half-life	8–17h	6–8h	Standard: 3–7h MR: 9–13h
Metabolism	CYP1A2, CYP2D6	glucuronide conjugation	CYP2D6 metabolism forms *O*-desmethylvenlafaxine (ODV)
Excretion	As metabolites: urine 70%, faecal 20% Unchanged: urine <1%	Unchanged: urine >50%	As metabolites: urine 80% Unchanged urine 5%

MR, modified release; PO, oral.

Table A.33 Interactions of SNRIs

Medications which alter duloxetine plasma levels	Pharmacodynamic interactions
Levels increased: duloxetine: ciprofloxacin and fluvoxamine; venlafaxine: clozapine and haloperidol	**With antiplatelets, anticoagulants, and NSAIDs:** increased risk of bleeding **With 5HT receptor agonists, e.g. SSRIs, TCAs, tramadol:** increased serotonergic side effects **With MAOIs/adrenaline/NA:** risk of hypertensive crisis. Do not start until at least 5 days after stopping duloxetine **With atomoxetine:** increased seizure risk **With methylthionium:** increased risk of CNS toxicity

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Statins

Statins are a group of widely used lipid-regulating drugs that work by inhibiting 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis. Statins have been demonstrated to have utility in the primary and secondary prevention of cardio-/cerebrovascular disease.

There are a number of statins of varying potencies available on the market. At present, atorvastatin, pravastatin, rosuvastatin, and simvastatin have evidence regarding their use in ischaemic stroke.

Currently, simvastatin and atorvastatin are the most frequently used agents in routine clinical practice. However, no studies have compared the relative efficacies of the different statins in ischaemic stroke.

Mechanism of action

All statins act by inhibiting HMG-CoA reductase, the rate-limiting enzyme of the HMG-CoA reductase pathway. This metabolic pathway is responsible for the hepatic production of cholesterol. This reduced hepatic cholesterol pool triggers increased expression of the LDL receptor and subsequent lowering of plasma LDL-cholesterol (LDL-C). The *SATURN* trial has also demonstrated that high-dose atorvastatin and rosuvastatin can lead to atheroma regression. Statins have also been demonstrated to exert additional pleiotropic effects, such as improving/restoring endothelial function and anti-inflammatory effects, and they may reduce the chance of developing AF. Thus, the effects of statins may reduce occlusive thrombotic events, irrespective of the initial cholesterol concentration.

All statins are given po in tablet form. They are typically given at night when peak cholesterol synthesis occurs. Little is known about IV administration of statins and their effects in the acute situation. However, a recent animal study that utilized IV rosuvastatin demonstrated protection from focal cerebral ischaemia for up to 4h after a cerebrovascular event. Thus, this is certainly a route of administration to be explored in future studies.

Toxicity and side effects

Statin-induced myopathy encompasses a wide clinical spectrum, ranging from myalgia (reported in up to 13% of patients commenced on statin therapy) to rhabdomyolysis. Muscle-related side effects have been demonstrated to have a higher prevalence with lipophilic statins (simvastatin, atorvastatin), in comparison to those with a hydrophilic structure (pravastatin, rosuvastatin).

- *Common—dermatological*: pruritus and rash. *Gastrointestinal*: abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, nausea, vomiting. *Immunological*: allergic reaction. *Musculoskeletal*: muscle cramps, myalgia, and myopathy. *Neurological*: dizziness, headache, and paraesthesiae. *Respiratory*: bronchospasm.
- *Serious—gastrointestinal*: hepatic failure, hepatitis, and pancreatitis. *Immunological*: angio-oedema. *Musculoskeletal*: rhabdomyolysis.

Statin therapy in acute ischaemic stroke

National recommendations, including NICE guidelines, advise that statins should be commenced 48h after the onset of ischaemic stroke.

The 48h delay before initiation of statins arose due to theoretical concerns of an increased risk of haemorrhagic conversion if used hyperacutely. This is based on the SPARCL trial of 2006, which suggested an increased risk of haemorrhagic stroke in those taking 80mg/day of atorvastatin, in comparison to placebo (2.3% vs 1.4%; $p = 0.002$). However, it is important to note that: (1) the benefits of atorvastatin on preventing further ischaemic strokes far outweighed the increased risk of haemorrhagic stroke, (2) post-hoc analysis demonstrated that increased risk was primarily observed in elderly men with a history of haemorrhagic stroke, (3) further meta-analyses have not shown any increased risk of ICH with statin use, following ischaemia, and (4) there is no direct evidence of harm in giving early statins in acute stroke.

Recent studies suggest that patients may benefit from statin treatment from stroke onset. A meta-analysis of 27 studies by Chroinin *et al*. demonstrated that patients who were on a statin prior to the onset of symptoms had improved functional outcome at 90 days (OR 1.41, 95% CI 1.29–1.56; $p < 0.001$). A significant reduction in mortality was reported at both 90 days (OR 0.71, 95% CI 0.62–0.82; $p < 0.001$) and at 12 months (OR 0.80, 95% CI 0.67−0.95; $p = 0.01$). Furthermore, Flint *et al*. demonstrated, in a retrospective analysis, that withdrawal of statin therapy following ischaemic stroke was associated with a significantly greater risk of death (hazard ratio 2.5, 95% CI 2.1–2.9; $p < 0.001$).

In conclusion, given the significant benefit demonstrated in these studies, patients already on statin therapy should continue on it, without interruption, following an acute stroke. For patients not previously on a statin, this is usually initiated at 48h, with further studies needed to assess if there is any added benefit from starting therapy *de novo* at stroke onset.

Statin therapy following intracerebral haemorrhage

It is unclear whether statins should be initiated in patients at high risk of ICH. Post-hoc analyses from the SPARCL trial and other studies suggest that statins may increase the risk of ICH in some patient groups, typically men who have already suffered from ICH. Having said this, several medium-sized meta-analyses have demonstrated that patients on statins prior to ICH have better outcomes and reduced mortality at 90 days. Furthermore, ICH survivors do not appear to be at increased risk of recurrence. A decision model created by Westover *et al*. suggested that, on the basis of available evidence, statins should be avoided in those with previous lobar ICH and used only with caution in those with previous 'deep' ICH.

Overall, given the current evidence, it appears sensible to exercise caution when utilizing statin therapy in those with previous ICH, particularly those of lobar location.

Monitoring

Caution should be exercised in patients with predisposing factors for rhabdomyolysis. In order to establish a reference baseline value, a CK level should be measured before starting a statin in the following situations: elderly (age ≥65 years), female gender, renal impairment, uncontrolled hypothyroidism, personal or family history of hereditary muscular disorders, previous history of muscular toxicity with a statin or fibrate and alcohol abuse. If muscle pain, weakness, or cramps occur, while a patient is receiving treatment with a statin, their CK levels should be measured. If these levels are found, in the absence of strenuous exercise, to be significantly elevated (>5 times the upper limits of normal), treatment should be stopped. If symptoms resolve and CK levels return to normal, then reintroduction of the statin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring. Those who experience sensitivity to one statin do not necessarily experience adverse effects with other statins.

LFTs should be measured before commencing treatment and be repeated at 3 and 12 months (unless there are clinical symptoms or signs of hepatotoxicity).

Contraindications

- *Absolute*: hypersensitivity to the drug or its excipients. Active liver disease or unexplained persistent elevations of serum transaminases that are >3 times the upper limit of the reference range. Pregnancy and lactation. Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin, and nefazodone). Acute porphyria.
- *Relative*: use statins with caution in those with risk factors for rhabdomyolysis or myopathy (personal or family history of muscle disorders, a high alcohol intake, renal impairment, hypothyroidism, and in the elderly). All statins should be used with caution in hepatic impairment.

Uses in special populations

- *Elderly*: the elderly have a higher risk of rhabdomyolysis and myopathy, and thus statins should be used cautiously and titrated carefully.
- *Pregnancy*: statins should be avoided in pregnancy, as congenital abnormalities have been reported and the reduction in cholesterol synthesis may affect fetal development. Thus, appropriate contraception is advised both during and for 28 days following cessation of treatment.
- *Lactation*: it is not known whether statins are present in breast milk. Manufacturers advise avoidance.

Efficacy

- *Atorvastatin*: the *SPARCL* (*S*troke *P*revention by *A*ggressive *R*eduction in *C*holesterol *L*evels) trial randomly assigned 4731 ambulatory patients with no known coronary heart disease (CHD) who had had a stroke or TIA within the preceding 6 months to treatment with either atorvastatin 80mg/day or placebo. Atorvastatin was associated with a reduction in

fatal or non-fatal stroke, as well as a significant reduction in all coronary events (5.2% vs 8.6%). Subgroup analysis of this study identified that, despite a relative reduction of non-fatal and fatal stroke by 21% in the group treated with atorvastatin (5-year absolute reduction in risk 2.2%; $p = 0.03$; unadjusted $p = 0.05$), there was a statistically significant difference in the incidence of intracranial haemorrhage (2.3% with atorvastatin vs 1.4% with placebo) between the two cohorts. However, post-hoc analysis of this study demonstrated that this increased risk was primarily observed in elderly men with a history of intracranial haemorrhage.

- *Simvastatin*: the *HPS* trial (*H*eart *P*rotection *S*tudy) enrolled 3280 adults with cerebrovascular disease who had previous non-disabling ischaemic stroke, TIA, and/or a history of carotid endarterectomy or angioplasty, but excluded patients who had had a stroke within 6 months. An additional 17 256 subjects with other occlusive arterial disease or diabetes were also enrolled. Patients were allocated to either 40mg simvastatin or placebo and monitored over a 5-year treatment period. Simvastatin treatment was associated with a significant reduction in all first stroke, compared with placebo (4.3% vs 5.7%), reflecting a 28% RRR in ischaemic strokes (p <0.0001).
- *Pravastatin*: in the CARE trial, pravastatin has being shown to reduce the incidence of stroke in patients who were prescribed pravastatin after MI. Compared with placebo, pravastatin resulted in a 27% reduction in stroke or TIA (95% CI 4–44%; $p = 0.02$).
- *Rosuvastatin*: the JUPITER study was a double-blind RCT that investigated the use of rosuvastatin in the primary prevention of cardiovascular disease. The trial appraised 17 802 patients with no previous history of cardiovascular disease and low-normal LDL-C but an elevated high-sensitivity CRP (hs-CRP) to either 20mg rosuvastatin or placebo. hs-CRP is a biomarker of inflammation and has shown to be an independent predictor of future vascular events (statin therapy has previously been shown to reduce hs-CRP levels). Rosuvastatin was shown to reduce LDL-C levels by 50% and reduce hs-CRP by 37%. Rates of stroke were found to be 0.18 and 0.34 per 100 person-years follow-up (48% relative risk reduction) in the rosuvastatin and placebo groups, respectively (hazard ratio 0.52, 95% CI 0.34–0.79).

Dosing and monitoring

- *Simvastatin*: following acute ischaemic stroke or TIA—start treatment at 40mg od.
- *Atorvastatin*: following acute ischaemic stroke or TIA—80mg od.
- *Pravastatin*: following acute ischaemic stroke or TIA—80mg od.
- *Rosuvastatin*: following acute ischaemic stroke or TIA—20mg od.

Pharmacokinetics and interactions

Pharmacokinetics See Table A.34.

Interactions See Table A.35.

Table A.34 Pharmacokinetics of statins

	Simvastatin	Atorvastatin	Pravastatin	Rosuvastatin
Main routes of administration	PO	PO	PO	PO
Oral bioavailability	60–80%	30%	34%	>10%
T_{max}	1.3–2.4h	2–3h	0.9–1.6h	3–5h
Protein binding	78–87%	>98%	50%	90%
Solubility	Fat-soluble	Fat-soluble	Water-soluble	Water-soluble
Pharmacologically active metabolites	Yes	Yes	No	Yes (minor)
Elimination half-life	2–3h	15–30h	1.3–2.8h	20.82h
Metabolism	CYP3A4	CYP3A4	Sulfation	CYP2C9, 2C19
Elimination	80% faeces, 13% urine	96% faeces, 2% urine	70% faeces, 20% urine	90% faeces, 10% urine

Table A.35 Interactions of statins

Medications which alter statin plasma levels	Medications whose plasma levels are altered by statins	Pharmacodynamic interactions
Levels decreased: CYP3A4/CYP2C9 inducers, e.g. carbamazepine, efavirenz, rifampicin, St John's wort, etc. **Levels increased:** CYP3A4/CYP2C9 inhibitors, e.g. indinavir, fluconazole, clarithromycin, and erythromycin	**Levels increased:** atorvastatin, coumarins, digoxin, ethinylestradiol, midazolam, and norethisterone	**With other agents that may cause myopathy, e.g. antiretrovirals, ciclosporin, corticosteroids, fibrates, etc.:** increased risk of myopathy **With antipsychotics, SSRIs, zidovudine, colchicine, and lithium:** increased risk of rhabdomyolysis

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Tricyclic antidepressants

TCAs are dibenzazepine derivatives of chlorpromazine. The first TCA imipramine was used in 1955. Due to their unfavourable side effect profile, they have largely been replaced by newer antidepressants for the treatment of depression, e.g. SSRIs and SNRIs. However, TCAs still have an important role in the treatment of several neurological conditions, including headache, insomnia, narcolepsy, and neuropathic pain. Notably, the analgesic and sedative effects desired in neurological conditions are often independent of their antidepressant effect. In general, the time to achieve an analgesic effect is days, compared to weeks for an antidepressant effect, and the effective dosage required is typically lower for many of the neurological indications.

There are a large number of different TCAs. Only those used in the management of neurological conditions are discussed further. These comprise clomipramine and imipramine, which preferentially inhibit 5HT reuptake; desipramine and nortriptyline, which preferentially inhibit NA reuptake; and amitriptyline, which produces a balanced inhibition of NA and 5HT reuptake. In addition to classification in terms of their pharmacological action, TCAs can also be grouped by their chemical structure. Amitriptyline, clomipramine, and imipramine are tertiary amines, whereas desipramine and nortriptyline are demethylation products of imipramine and amitriptyline, respectively, and are hence termed secondary amines.

Which tricyclic antidepressant to use?

Amitriptyline has been used in the majority of trials for neuropathic pain and therefore has the biggest evidence base and is often used first-line. If amitriptyline fails, due to intolerable side effects, NICE guidance recommends switching to an alternative TCA such as nortriptyline. All TCAs have a similar side effect profile however, nortriptyline is generally better tolerated than amitriptyline, particularly in the elderly, as it causes less sedation and dry mouth. However, if one TCA is ineffective, rather than not tolerated, then NICE recommends a trial of a drug from a different class, e.g. an antiepileptic.

Uses

Licensed uses

In the UK/USA

1. *Amitriptyline* is licensed for a wide range of psychiatric disorders. There are no licensed neurological uses.
2. *Clomipramine* is licensed as an adjunct in the management of cataplexy associated with narcolepsy in individuals aged 18 years and older in the UK. In the USA, clomipramine has no licensed neurological indications.
3. *Desipramine* is licensed for a wide range of psychiatric disorders. There is no licensed neurological use, and desipramine is no longer marketed in the UK.
4. *Imipramine* is licensed for a wide range of psychiatric disorders, as well as childhood enuresis. There is no licensed neurological use.
5. Nortriptyline is licensed for a wide range of psychiatric disorders. There are no licensed neurological uses.

Off-licence uses

1. *Amitriptyline*: insomnia, MOH, neuropathic pain, and the prophylaxis of migraine and TTH.
2. *Clomipramine/despiramine/imipramine*: migraine prophylaxis and neuropathic pain.
3. *Nortriptyline*: neuropathic pain and prophylaxis of migraine and TTH.

Mechanism of action

The majority of TCAs work as 5HT and NA reuptake inhibitors, increasing synaptic levels of these neurotransmitters. They also have a broad but variable spectrum of activity at multiple other receptors, including action as antagonists at serotonin receptors, α1-adrenergic receptors, NMDA receptors, H1 and H2 histamine receptors, and muscarinic acetylcholine receptors, and as agonists at sigma receptors. Actions at these sites contribute to their significant side effect profile. Most TCAs also potently inhibit sodium channels and L-type calcium channels, which causes cardiotoxicity and a high mortality rate in overdose.

- *Headache/narcolepsy/neuropathic pain*: it is unclear how TCAs reduce the severity of headache and neuropathic pain, or reduce the incidence of cataplexy. Their action is likely to be multimodal by interaction in the aforementioned neurotransmitter pathways. In neuropathic pain, they may modulate neurotransmission of the descending pain pathways and thus inhibit nociceptive signals, while, in headache, they are believed to reduce the cortical spreading depression seen in migraine.
- *Insomnia*: the sedating effect of amitriptyline is predominantly mediated by its antihistamine action at the H1 receptor. It may also promote sleep by antagonistic effects at 5HT2 and muscarinic receptors. Treatment of underlying anxiety and depression may also contribute, as these are frequently associated with insomnia, although doses used in insomnia are much reduced, compared to doses used routinely in the treatment of these conditions.

Toxicity and side effects

- *Common—antimuscarinic*: blurred vision, constipation, dry mouth, urinary retention. *Neurological*: dizziness, drowsiness, paraesthesiae. *Psychiatric* (particularly in the elderly): agitation, anxiety, confusion, sleep disturbance, irritability.
- *Serious—cardiovascular*: arrhythmia, heart block, risk of cardiotoxicity, and death in overdose. *Gastrointestinal*: paralytic ileus. *Haematological*: desipramine has been reported to cause agranulocytosis. *Neurological*: convulsions, NMS.

Contraindications

- *Absolute*: immediate recovery from MI, arrhythmias, acute mania, acute porphyria. Desipramine is contraindicated in patients with a family history of sudden cardiac death.
- *Relative*: TCAs reduce the seizure threshold and can exacerbate prostatic hypertrophy, urinary retention, and angle-closure glaucoma. They should be avoided with tramadol, due to the risk of serotonin syndrome (rare). TCAs should be started with care in patients with phaeochromocytoma, hyperthyroidism, and diabetes.

No dose alteration is required in hepatic or renal impairment.

Uses in special populations

- *Elderly*: the elderly are more susceptible to anticholinergic systemic and cognitive side effects, and benefit from lower dosing regimens.
- *Pregnancy*: no proven reported side effects when used in pregnancy, but limited evidence. Use if benefit outweighs risk.
- *Lactation*: present in low quantities in breast milk. There is limited evidence for neonatal side effects with any of the TCAs.

Efficacy

1. Amitriptyline.
   - *Headache*: amitriptyline has been shown to be consistently effective in *migraine* prophylaxis but, due to its side effect profile, is a second-line agent. In a systematic analysis of four RCTs, amitriptyline was found to be more effective than placebo in all the trials. It significantly reduced the number of headache days by 6.9 for TTH and 1.4 for migraine. In *TTH*, amitriptyline is a first-line agent, with one RCT (n = 203) demonstrating that headache severity was significantly reduced in 38% of patients on amitriptyline, compared to 29% with placebo. In *MOH*, amitriptyline has been shown to be effective in open-label studies, but superiority over placebo has not been shown in RCTs. In an RCT, it was shown to non-significantly reduce headache, when compared to placebo (45% vs 28%; p = 0.3).
   - *Insomnia*: no controlled studies have been undertaken. Evidence for use of amitriptyline in insomnia is predominantly based on expert consensus guidelines and known sedative side effects identified from studies of its action in mood disorders.
   - *Neuropathic pain*: the effectiveness of amitriptyline in neuropathic pain has been established through a number of systematic reviews. In one systematic review, involving ten studies with a total of 588 patients suffering from diabetic neuropathic pain, post-herpetic neuralgia, or cancer neuropathic pain, the NNT was 3 (95% CI 2.5–4.2). A further systematic review evaluated the use of amitriptyline in the management of diabetic neuropathy, fibromyalgia, post-herpetic neuralgia, and post-stroke pain in a total of 687 participants over eight studies. The NNT was 4.6 (95% CI 3.6–6.6).
2. Clomipramine.
   - *Narcolepsy*: evidence for use of clomipramine in the treatment of cataplexy is mostly based on case studies. One small comparative cross-over study compared clomipramine with fluvoxamine in the management of narcolepsy and demonstrated, out of 11 patients treated with clomipramine, ten of these patients demonstrated some improvement in frequency of cataplexy attacks. In four of these patients, attacks of cataplexy ceased altogether, and there was a >50% reduction in cataplexy attacks in a further three patients. Sleep paralysis was also dramatically reduced; however, there was little improvement in excessive daytime sleepiness. Numbers were insufficient to suggest which out of clomipramine and fluvoxamine was the more effective drug.

- *Neuropathic pain*: the efficacy of clomipramine has only been studied in small clinical trials. One such study of 19 patients showed a significant reduction in all patients' report of neuropathic pain in diabetic neuropathy, with a 39% reduction in pain score, compared to placebo ($p < 0.05$).

3. *Desipramine*: a systematic review identified two studies, involving 100 patients, demonstrating that desipramine offers pain relief to patients with post-herpetic neuralgia. The NNT was 2.6 (95% CI 1.9–4.5).
4. *Imipramine*: evidence for the effect of imipramine in treating neuropathic pain has been summarized in a systematic review. This included three studies investigating the use of imipramine in 114 patients with painful diabetic neuropathy. The NNT was 2.2 (95% CI 1.7–3.22).
5. *Nortriptyline*.
   - *Headache*: there is no trial evidence to support the use of nortriptyline in the prophylaxis of migraine or TTH. However, it is the active metabolite of amitriptyline and hence thought to be similarly effective. In addition, when compared to amitriptyline, it has a more favourable side effect profile, with less sedation and weight gain.
   - *Neuropathic pain*: two cross-over studies have looked at nortriptyline in the treatment of post-herpetic neuralgia. One study compared the efficacy of nortriptyline to amitriptyline and found both to be equally effective, providing 21 of the 33 participants with moderate pain relief. Another study of 71 patients compared desipramine or nortriptyline treatment to placebo for painful herpetic neuralgia. The individual TCAs were not analysed separately, but a significant reduction in pain was found overall with both treatments. The NNT was 4.0 (95% CI 2.6–8.9).

Dosing and monitoring

Dosing

- *Neuropathic pain*: is the same for all TCAs—starting dose: 10mg at night. Increase by 25mg every 3–7 days. Maximum dose 150mg daily. Greater than 75mg requires specialist supervision. Trial for 6–8 weeks, with at least 2 weeks at the maximum tolerated dose.

1. Amitriptyline.

- *Headache*: start treatment at 10mg, given at night. This can be increased at weekly/fortnightly intervals by 10–25mg to 50–100mg at night, according to response. The maximum recommended dose is 150mg for migraine and 50mg in MOH.
- *Insomnia*: 10mg or 25mg given at night. This has been used for long periods.

2. Clomipramine.

- *Narcolepsy*: start treatment at 10mg od at night; this can be increased up to a maximum of 75mg/day in divided or single doses gradually over a course of 2 weeks. Low doses (≤20mg) are often effective.

3. Nortriptyline.

- *Headache*: the starting dose is 10–25 mg at night, increased at weekly/fortnightly intervals by 10–25mg, according to response. The therapeutic dose ranges from 10mg to 150mg daily. It can be given in divided doses.

Routine monitoring

None routinely required. In patients who have, or are at risk of, cardiovascular disease, consider baseline ECG/repeat ECG at dose changes. TCAs should be withdrawn gradually to avoid discontinuation side effects.

Pharmacokinetics and interactions

Pharmacokinetics See Table A.36.

Interactions See Table A.37.

Table A.36 Pharmacokinetics of TCAs

	Amitriptyline	Clomipramine	Desipramine	Imipramine	Nortriptyline
Main routes of administration	PO	PO	PO	PO	PO
Oral bioavailability	30–60%	50%	73–92%	94–96%	51%
T_{max}	4h	2–6h	2–6h	2–6h	5h
Protein binding	96%	97–98%	73–92%	86%	93–95%
Time to steady state	3–8 days	3 weeks	19 days	19 days	10–14 days
Pharmacologically active metabolites	Yes, strong	Yes, strong	No	Yes, strong	Yes, strong
Elimination half-life	30h	21–36h	15–24h	20h	8–28h
Metabolism	CYP2D6, CYP2C19	CYP2D6, CYP2C19	CYP2D6	CYP2D6, CYP2C19	CYP2D6
Excretion	Urine 95%	Urine 60%, faeces 30%	Urine 70%	urine 80%, faeces 20%	Urine 90%, faeces 10%

PO, oral.

Most TCAs undergo extensive hepatic first-pass metabolism, a large volume of distribution, and binding to plasma proteins. All TCAs are metabolized by P450 2D6. Seven to 10% of Caucasians are poor metabolizers. Any drug that interacts with P450 2D6 will alter the plasma concentration of TCAs.

Table A.37 Interactions of TCAs

Medications which alter TCA plasma levels	Pharmacodynamic interactions
Levels decreased: carbamazepine, phenobarbital, phenytoin, St John's wort Levels of sublingual medications, e.g. nitrates, are reduced due to poor absorption with dry mouth **Levels increased:** CYP2D6 inhibitors, e.g. antipsychotics and SSRIs	**With CNS depressants, e.g. alcohol, antihistamines, anxiolytics, and opioids:** enhanced sedative side effects **With methylthioninium, rasagiline, selegiline, and tramadol:** increased CNS side effects **With MAOI:** TCAs should not be started until 2–3 weeks after stopping an MAOI. MAOIs should not be started for 1–2 weeks after stopping a TCA **With antiarrhythmics, e.g. amiodarone, disopyramide, flecainide, sotalol; antimicrobials, e.g. moxifloxacin; antipsychotics, e.g. droperidol and pimozide; antivirals, e.g. saquinavir; and sympathomimetics:** increased risk of arrhythmias **With hypotensive agents:** increased risk of low BP **With antimuscarinic agents, e.g. antihistamines:** increased antimuscarinic side effects **With lithium:** increased toxicity

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Triptans

The triptans are a large group of 5HT agonists, which have been shown to be highly effective in the treatment of migraine and cluster headache. There are a number of triptans available, the advantages and disadvantages for which are outlined in Table A.38.

Uses

Licensed uses

In the UK

- *Migraine*.
  1. *Almotriptan* is licensed for the acute management of migraine (with or without aura) in individuals aged 18 years and older.

Table A.38 Advantages and disadvantages of different triptan medications

	Preparations	Advantages	Disadvantages
Almotriptan	12.5mg tablet	Highest bioavailability, lower incidence of chest pain	Renally excreted—needs dose reduction in renal impairment
Eletriptan	40mg tablet	Most effective triptan	Has the most side effects. Not licensed for use in the >65s
Frovatriptan	2.5mg tablet	Licensed for MAM, prolonged therapeutic effect (long half-life), possible better cardiovascular risk profile	Theoretical risk of ophthalmic toxicity. Not licensed for use in the >65s
Naratriptan	2.5mg tablet	Licensed for MAM, better side effect profile	Slow onset of action, dose reduction in renal impairment. Not licensed for use in >65s
Rizatriptan	10mg dispersible/ standard tablet	Dispersible tablet useful if nausea and vomiting during attacks	Dose reduction in renal impairment
Sumatriptan	Oral tablet: 50mg Nasal spray: 5-20mg SC injection: 6mg	Most supportive evidence. Multiple routes of administration	Not licensed for use in the >65s
Zolmitriptan	Dispersible and standard tablet and nasal spray: 2.5mg	Rapidly absorbed, licensed for adolescents, licensed for MAM	Not licensed for use in the >65s

In the USA

- *Migraine*.
  1. *Almotriptan* is licensed in the acute management of migraine (with or without aura) in individuals aged 12 years and older who experience migraine lasting ≥4h without treatment.

In the UK/USA

(Licensing is the same.)

- *Migraine*.
  1. *Eletriptan* is licensed for the acute treatment of migraine (with or without aura) in individuals aged between 18 and 65 years of age.
  2. *Frovatriptan* is licensed for the acute treatment of migraine (with or without aura) in individuals aged between 18 and 65 years of age.
  3. *Naratriptan* is licensed for the acute treatment of migraine (with or without aura) in individuals aged between 18 and 65 years of age.
  4. *Rizatriptan* is licensed for the acute management of migraine (with or without aura) in individuals aged 18 years and older (UK) and in individuals aged 6 years and older (USA).
  5. *Sumatriptan* is licensed for use in the acute management of migraine (with or without aura) in individuals aged between 18 and 65 years. The SC injection is also licensed for use in the acute management of cluster headache.
  6. *Zolmitriptan* is licensed for the acute management of migraine (with or without aura) in individuals aged between 18 and 65 years of age.

Off-licence uses

- None.

Mechanism of action

Triptans are believed to have a variety of targets in the CNS. They are thought to cause cerebral vasoconstriction, most likely via activation of $5HT_{1B}$ receptors present on the smooth cells of the cerebral vasculature. They are also believed to act on $5HT_{1D}$ receptors present on trigeminal neurons, thus preventing the release of vasoactive peptides. They may also block the transmission of nociceptive signals from reaching the thalamus through activity at $5HT_{1D}$ receptors in the dorsal horn.

Toxicity and side effects

- *Common—cardiac*: the 'triptan sensations' are a constellation of adverse effects commonly experienced with triptan administration. They include flushing, dizziness, and transient throat and chest tightness. *Dermatological*: injection site reactions include bleeding, bruising, and erythema. *Gastrointestinal*: epistaxis (nasal spray), diarrhoea, nausea, unpleasant taste. *Neurological*: paraesthesiae may be experienced as part of the triptan sensations.
- *Serious—cardiac*: arrhythmias, myocardial ischaemia. *Gastrointestinal*: bowel obstruction, deranged LFTs, mesenteric ischaemia. *Immunological*: anaphylaxis.

Contraindications

- *Absolute*: history of coronary vasospasm, ischaemic heart disease, MI, hepatic or renal failure, severe hypertension, stroke, or TIA. Hypersensitivity to triptans or any of their components is also a contraindication. Triptans should not be used in hemiplegic or basilar migraines.
- *Relative*: triptans can be used in elderly patients but are unlicensed and should be used with caution.

Uses in special populations

- *Elderly*: triptans should be used with caution in the elderly, due to the increased prevalence of cardiovascular disease in this group. Almotriptan and rizatriptan, although efficacy and safety are not well established, can be used in individuals aged ≥65 years. Eletriptan, frovatriptan, naratriptan, sumatriptan, and zolmitriptan are not licensed for patients aged ≥65 years, due to a lack of efficacy and tolerability data.
- *Pregnancy*: in animal studies, almotriptan, naratriptan, and rizatriptan have been shown to cause fetal harm, but there have been no confirmed cases of harm to a human fetus. There are limited data on the safety of the other triptans. The current recommendation is that the triptans should only be used in pregnancy if the expected benefit outweighs the risk of harm.
- *Lactation*: the triptans are all present in breast milk, but in quantities thought to be too small to be harmful. The current advice is that breastfeeding should be stopped until 24h (12h for sumatriptan) after the last dose was taken.

Efficacy

1. *Almotriptan: migraine*—in a randomized, double-blind study of almotriptan (6.25mg and 12.5mg) vs placebo, both doses of almotriptan were found to be more effective than placebo at reducing the severity of attacks at 2h (number of attacks relieved 60% and 70% vs 38%, respectively; $p < 0.001$), and less than one-third of patients had headache recurrence in 24h. Almotriptan was also well tolerated, with no significant difference in adverse effects between treatment and placebo groups. The 12.5mg dose was found to be the most efficacious, with few additional adverse effects, compared with the lower dose.
2. *Eletriptan: migraine*—20mg, 40mg, and 80mg doses were found to be superior to placebo at reducing headache severity at 2h in several RCTs. Eletriptan 20mg has a similar efficacy to sumatriptan 100mg, while the higher doses 40mg and 80mg were found to be superior to sumatriptan 100mg at reducing headache severity at 2h and at maintaining a sustained response at 24h. Cost-effectiveness of the 40mg dose was felt to be equivalent to sumatriptan 50mg or 100mg. It is generally well tolerated, with commonly reported side effects including nausea, drowsiness, and dizziness (similar to other triptans). The 80mg dose had a greater rate of adverse events than sumatriptan, while the other doses (20mg and 40mg) produced a comparable rate of adverse events to sumatriptan.

3. *Frovatriptan: migraine*—there have been several RCTs comparing frovatriptan 2.5mg with placebo in migraine. All have demonstrated a clear benefit of frovatriptan. Response rates for frovatriptan have ranged from 37% to 53%, compared with 21–34% with placebo. Patients were significantly more likely to be pain-free with frovatriptan, compared with placebo (9–19% vs 2–6%, respectively). In comparisons with almotriptan and rizatriptan, frovatriptan was significantly less likely to result in headache recurrence at 48h (27% for frovatriptan vs 49% for other triptans; $p < 0.001$). Frovatriptan was generally well tolerated, with only 1% of patients stopping the drug because of adverse effects. Side effects were similar to other triptans and included dizziness, fatigue, and numbness.
4. *Naratriptan: migraine*—2.5mg and 1mg have been shown to be superior to placebo in several RCTs. In one trial, headache relief at 4h was reported in 60% of patients taking 2.5mg of naratriptan, compared with 50% for 1mg and 34% for placebo (2.5mg and 1mg vs placebo, $p < 0.05$). Efficacy of naratriptan is measured at 4h due to its longer onset of action. Naratriptan 2.5mg has been shown to be less effective than sumatriptan 50mg or 100mg but has fewer side effects. It has the lowest rate of migraine recurrence of the triptans (excluding frovatriptan). An advantage of naratriptan is its tolerability, with a similar side effect profile to placebo.
5. *Rizatriptan: migraine*—a Cochrane review of rizatriptan in acute migraine found that both the 5mg and 10mg doses were superior to placebo in all endpoints. For headache reduction at 2h, the NNT for 5mg was 3.9 (3.3–4.7), and for 10mg 2.7 (2.4–2.9). A dose–response relationship was demonstrated, with the 10mg dose showing greater efficacy, than 5mg. Compared with other triptans, rizatriptan is the second most effective at reducing headache severity at 2h (after eletriptan).
6. *Sumatritan: migraine*—a Cochrane review of the use of oral sumatriptan in migraine found that both the 25mg and 50mg doses of sumatriptan were superior to placebo in achieving a pain-free state at 2h. The NNT was 6.1. The 100mg dose was superior to both placebo and the lesser doses, reducing pain from moderate/severe to nil at 2h in 32% of patients, compared with 11% for placebo. SC sumatriptan is sometimes preferred in the acute management of migraine, due to delayed gastric emptying and nausea and vomiting. A Cochrane review of SC sumatriptan found it to be superior to placebo for all outcomes. 59% of patients were pain-free at 2h after a single 6mg dose of sumatriptan, compared with 15% with placebo. It is also more effective than the oral equivalent but associated with a higher incidence of side effects. Intranasal sumatriptan has a quicker onset of action than the oral equivalent and fewer side effects. *Cluster headache*—SC sumatriptan has been shown in randomized, placebo-controlled trials to be effective at reducing cluster headache pain at 30min in about 75% of patients. Sumatriptan nasal spray is also effective in cluster headache. In a Cochrane review of triptans in cluster headache, the NNT with SC sumatriptan 6mg for headache freedom at 15min was 3.3.

7. *Zolmitriptan*: oral zolmitriptan has been shown to be more effective than placebo in a number of RCTs. In one trial comparing zolmitriptan with placebo, all doses of zolmitriptan were more effective than placebo at reducing migraine severity at 2h (53–67% vs 34%, respectively; p <0.001). Complete headache resolution was more likely with the higher doses of zolmitriptan (≥2.5mg). The higher doses were associated with a higher rate of adverse events, but there were no reports of serious side effects. In trials comparing triptans, zolmitriptan 5mg had a similar efficacy to sumatriptan 100mg but was more effective than the lower doses of sumatriptan (25mg and 50mg). The dispersible tablets are useful in patients who are unable to take oral tablets because of nausea and vomiting, but there is no evidence that they work faster than the standard tablets. A Cochrane review concluded that zolmitriptan nasal spray in cluster headache was more effective than placebo at achieving pain freedom at 15min (NNT 11, 6.4–49) but was less effective than SC sumatriptan.

Dosing and monitoring

1. *Almotriptan*: a single dose of 12.5mg should be given at the beginning of the migraine. If the headache recurs, a repeat dose can be given after 2h. The maximum dose of 25mg should not be exceeded within 24h. If there is no effect with the initial dose, a repeat dose should not be given.
2. *Eletriptan*: 40mg of eletriptan should be given at the beginning of headache onset. If headache continues, then a repeat 40mg dose can be give 2h after the initial dose. No more than 80mg should be given in 24h. Some patients may require an initial dose of 80mg. If there is no response to the first dose, a repeat dose should not be given.
3. *Frovatriptan*: 2.5mg should be given as soon as possible after the headache has started. If it recurs, a repeat dose can be given 2h after the initial dose. No more than 5mg to be given in 24h. If there is no response to the first dose, a second dose should not be given.

   For MAM, 2.5mg should be started bd 2 days before the onset of menstruation and should be continued for a total of 6 days.
4. *Naratriptan*: 2.5mg should be given as early as possible at the onset of headache. If headache recurs, a repeat dose can be given at least 4h after the initial dose. If there is no response to the first dose, a repeat dose should not be given.

   For MAM, 1mg should be started bd 2 days before the onset of menstruation and should be continued for 5 days.
5. *Rizatriptan*: 10mg should be given as soon as possible after the onset of headache. A repeat dose can be given at least 2h after the initial dose if headache recurs. A second dose should not be given if there is no response to the first dose. The maximum dose in 24h is 20mg in the UK and 30mg in the USA. If the patient is also taking propranolol, both the dose given to terminate and the maximum dose in 24h should be halved.

6. *Sumatriptan—oral*. UK: the initial dose is 50mg. This can be repeated at 2h if there is some response to the first dose but the pain recurs. Some patients may require an initial dose of 100mg. The maximum dose in 24h is 300mg. USA: an initial dose of 25mg is recommended, with a maximum dose in 24h of 200mg. A repeat dose should not be taken if there has been no response to the first dose. *SC*: for the SC route, 6mg should be given for both migraine and cluster headache. This dose can be repeated after 1h if headache returns; no more than 12mg should be given in 24h. *Intranasal*: the dose is typically a single dose of 5–20mg, repeated at 1h if there is headache recurrence. No more than 40mg should be given intranasally in 24h.
7. *Zolmitriptan*: 2.5mg should be given as soon as possible after the onset of headache. A repeat dose can be given 2h after the initial dose if headache recurs. Some patients may require an initial dose of 5mg. A second dose should not be given if there is no response to the first dose. The maximum dose in 24h is 10mg.

   For MAM, 2.5mg should be started bd to tds 2 days before the onset of menstruation and should be continued for 7 days (5 days after the start of menses).

   With the nasal spray, one spray of 2.5mg or 5mg should be given into one nostril and should only be repeated after 2h if headache recurs. The maximum dose is 10mg in 24h.

   If the patient is also taking cimetidine, the maximum dose in 24h is 5mg.

Routine monitoring

Patients should be monitored for cardiac adverse effects, notably chest/throat tightness. If severe, triptan should be discontinued. If there are risk factors for ischaemic heart disease, an ECG should be considered before commencement.

Pharmacokinetics and interactions

Pharmacokinetics See Table A.39.

Interactions See Table A.40.

As a rule, the triptans undergo hepatic metabolism, are eliminated mainly by the renal system, and do not display induction of liver enzymes. Eletriptan and frovatriptan are exceptions—10% and 36% renally excreted, respectively. Almotriptan, naratriptan, sumatriptan, and zolmitriptan are not affected by food ingestion. The peak concentration of eletriptan is increased 20–30% with a high-fat meal. The time to peak of frovatriptan and rizatriptan is delayed by 1h if given with food, but there is no effect on bioavailability.

Table A.39 Pharmacodynamics of triptans

	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan
Main routes of administration	PO	PO	PO	PO	PO	IN/PO/SC	IN/PO
Bioavailability	~70%	50%	20% in men, 30% in women	70%	40–45%	16% IN 14% PO 97% SC	40% PO 100% IN
T_{max}	1–3h	0.75–1.5h (2.8h in migraine)	2–4h	2–3h (3–4h in migraine)	1–2.5h	1.5h IN, 2h PO, 25min SC	3h IN, 1.5–3h PO
Protein binding	35%	85%	15%	28–31%	14%	14–21%	25%
Pharmacologically active metabolites	No	Yes, weak	Yes, weak	No	No	No	Yes, strong
Elimination half-life	3.5h	4h	26h	6h	2–3h	2h	2.5–3h

IN, intranasal; PO, oral; SC, subcutaneous.

Table A.40 Interactions of triptans

Medications which alter triptan plasma levels	Pharmacodynamic interactions
Levels increased: Almotriptan: azole antifungals, fluoxetine, ritonavir, verapamil Eletriptan: macrolide antibiotics, ritonavir Frovatriptan: oral contraceptives, propranolol Rizatriptan: propranolol Zolmitriptan: cimetidine, moclobemide, quinolone antibiotics **Levels decreased:** Frovatriptan: ergotamine	**With ergot alkaloids**: triptans should not be given within 24h of receiving this class of compounds; increased risk of vasospasm **With metoclopramide and SSRIs/SNRIs**: avoid concomitant use due to risk of serotonin syndrome **With MAOIs**: increased risk of toxicity; avoid for 2 weeks after MAOIs stopped

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Typical antipsychotics

Typical antipsychotics are characterized by their propensity to cause extrapyramidal side effects. This gave rise to the name 'neuroleptics', meaning to 'seize the neuron'. In addition to the treatment of psychosis, these agents are used to treat severe tics, chorea, and behavioural disturbance associated with late-stage neurodegenerative disease such as dementia.

Uses

Licensed uses

In the UK/USA

- *Tic disorders*.
  1. *Haloperidol*: is licensed for the treatment of severe tics and TS in individuals aged 3 years and older (UK), and 18 years and older (USA).

In the USA

- *Tic disorders*.
  1. *Pimozide*: is licensed for the treatment of motor and phonic tics in TS in individuals who have not responded adequately to first-line therapy in individuals aged 12 years and older.

Pimozide is used in the management of psychotic disorder but has no licensed neurological use in the UK.

Off-licence uses

1. *Haloperidol*: chorea.
2. *Sulpiride*: chorea, tics, and TS.

Mechanism of action

Their action in TS and other tic disorders is thought to be the result of dopamine (D2) receptor antagonism. A lower affinity for H1 histaminergic and α2-adrenergic receptors means these drugs cause less sedation, orthostatic hypotension, and weight gain than atypical antipsychotics. There is, however, a greater incidence of extrapyramidal side effects.

Toxicity and side effects

- *Common—cardiovascular*: orthostatic hypotension. *Dermatological*: rash. *Endocrine*: hyperprolactinaemia and menstrual disorder. *Gastrointestinal*: constipation, dry mouth, nausea, vomiting, and weight gain. *Neurological*: dizziness, extrapyramidal symptoms (tardive dyskinesia and parkinsonism), insomnia, and sedation. *Urological*: erectile dysfunction, urinary retention.
- *Serious—cardiovascular*: prolonged QT and VTE. *Neurological*: NMS. *Respiratory*: bronchospasm.

Contraindications

- *Absolute*: hypersensitivity to drug or its excipients, prolonged QT, and co-administration with medications known to prolong the QT interval (e.g. TCAs). Haloperidol should also be avoided in CNS depression, PD, and other lesions of the basal ganglia.

- *Relative*: epilepsy (reduction in seizure threshold). Caution should be taken in hepatic and renal impairment. Start with small doses, and increase slowly.

Uses in special populations

- *Elderly*: no dosage alteration is routinely recommended; however, the elderly are more prone to orthostatic hypotension, and trials of antipsychotics in elderly patients with dementia have suggested that there is an increased incidence of cerebrovascular events.
- *Pregnancy*: adverse events have been noted in animal studies; however, teratogenicity has not been identified so far in limited human data. Neonates born to mothers taking antipsychotics may exhibit extrapyramidal side effects or withdrawal. Typical antipsychotics should only be used in pregnancy if the benefits outweigh the risks.
- *Lactation*: all of the typical antipsychotics mentioned are excreted in breast milk; the manufacturers recommend avoidance by nursing mothers.

Efficacy

1. *Haloperidol*: a double-blind, placebo-controlled RCT ($n = 57$) established that both haloperidol and pimozide were effective in controlling tic disorders. Due to similar efficacy and better tolerability, pimozide is often used first-line. Greater than 70% of tic suppression can be anticipated in approximately two-thirds of patients with either of these agents.
2. *Pimozide*: a Cochrane review of six RCTs found pimozide to be more effective than placebo, slightly less effective than haloperidol, but also associated with fewer side effects. It was as effective as risperidone, with no significant difference between side effect profiles.
3. *Sulpiride*: short-term sulpiride treatment for TS in children and adolescents was assessed over 6 weeks in a recent open-label prospective trial ($n = 189$). The trial reported significant reduction in vocal (64%) and motor (49%) tics and in the total Yale Global Tic Severity Score (59%) score ($p < 0.05$). In addition to its efficacy in tic disorders, small studies have suggested that its mood-stabilizing and antidepressant effects may also be useful in the management of co-morbid obsessive–compulsive disorder.

Dosing and monitoring

1. *Haloperidol*: start treatment at 0.25–0.5mg/day in two divided doses, and increase gradually, as required/tolerated, to a usual maintenance dose of 0.5–3mg/day in 2–3 divided doses. The maximum recommended dose is 6mg.
2. *Pimozide*: start treatment at 1–2mg/day in divided doses. Increase by 1mg every other day, as required/tolerated, to a usual maintenance dose of 6–8mg/day. The maximum recommended dose is 10mg/day.
3. *Sulpiride*: start treatment at 50–100mg/day, and increase every 2–4 weeks by 100–200mg, as required/tolerated. The usual maintenance dose is 100–400mg bd. The maximum recommended dose is 2g.

Routine monitoring An ECG should be performed at baseline. Monitor BMI, BP, FBC, glucose, and thyroid, renal, and liver function, as well as lipid panels, on a regular basis.

Pharmacokinetics and interactions

Pharmacokinetics See Table A.41.

Interactions See Table A.42.

Table A.41 Pharmacokinetics of typical antipsychotics

	Haloperidol	Pimozide	Sulpiride
Main routes of administration	IM, IV, PO	PO	PO
Oral bioavailability	60%	50%	25–40%
T_{max}	2–6h	6–8h	2–6h
Protein binding	92%	99%	40%
Metabolism	Hepatic CYP3A4	Hepatic CYP3A4, CYP1A2, CYP2D6	Minimal metabolism
Pharmacologically active metabolites	No	Undetermined	No
Elimination half-life	18h	55h	6–8h
Excretion	Urine (30%), faeces (20%)	Urine	95% urine and faeces unchanged

PO, oral.

Table A.42 Interactions of typical antipsychotics

Medications which alter typical antipsychotic* plasma levels	Pharmacodynamic interactions
Levels decreased: CYP3A4 and CYP2D6 inducers **Levels increased:** CYP3A4 and CYP2D6 inhibitors (dependent on method of metabolism; see pharmacokinetics in Table A.41)	**With CNS depressants, e.g. alcohol:** enhanced sedative effects **With agents known to prolong QTc, e.g. chlorpromazine and macrolide antibiotics:** increased risk of ventricular arrhythmia **With other antipsychotics (e.g. atypicals)/ tetrabenazine:** may increase the risk of extrapyramidal side effects **With antihypertensive agents:** increased risk of hypotension

* Haloperidol, pimozide, and sulpiride.

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Z-Drugs

The Z-drugs are a group of hypnotic benzodiazepine-like drugs that were first marketed in the 1980s. They share a similar mechanism of action and side effect profile to benzodiazepines. They were initially marketed as benzodiazepine alternatives with what was thought to be lower risks of dependence and tolerance; however this has not been borne out in clinical trials. Physical and psychological dependence can occur with therapeutic use of any of the Z-drugs. As a result courses should be kept to a minimum duration, ideally less than 2 weeks including taper. Meta-analyses and reviews conducted so far have suggested that there is little additional benefit from the use of Z-drugs compared to short acting benzodiazepines such as temazepam, although well controlled comparative studies are rare.

There is significant difference in the half-lives of different Z-drugs which gives them their different uses in insomnia. Zaleplon and unmodified zolpidem have very short half-lives making them useful in sleep initiation insomnia. Zaleplon can also be used in patients with early awakening as it can be taken closer towards morning than other drugs with minimal effects on next day cognitive ability. In contrast modified release zolpidem and zopiclone have longer half-lives. This makes them useful agents in the management of patients with sleep initiation and sleep maintenance insomnia.

Eszopiclone and Zopiclone

Zopiclone is a racemic mixture of 2 stereoisomers, only one of which is pharmacologically active. It was initially classified as a schedule IV controlled substance in the USA due to its addictive properties and hence not licensed for therapeutic use. In 2005 the isolated active stereoisomer: termed eszopiclone was licensed in the USA—little is known about the clinical differences, other than dosing, between the two drugs. In light of their pharmacological similarities they are believed to be alike in most respects.

Uses

Licensed uses

In the UK

Insomnia:

1. Zaleplon and Zolpidem are licensed for the management of insomnia associated with difficulty falling asleep where this disorder is severe enough to be disabling or cause the individual extreme distress, in individuals aged >18 year old.
2. Zopiclone is licensed for the short-term treatment of insomnia, including difficulties getting to sleep, maintaining sleep, and waking early in situations where insomnia is debilitating or causes severe distress, in individuals aged >18 years old.

In the USA
1. Eszopiclone is licensed for the treatment of insomnia in individuals aged >18 years old.
2. Zaleplon: is licensed for the short term treatment of insomnia in individuals aged >18 years old.
3. Zolpidem (license varies depending on formulation—all for adults >18 years old): Ambien®: short-term treatment of insomnia where there is difficulty of sleep initiation. Ambien CR®: short term treatment of insomnia where there is difficulty of sleep onset or sleep maintenance. Intermezzo® (sublingual): short-term treatment of insomnia where middle-of-the night wakening is associated with difficulty returning to sleep, provided there are 4h of bedtime remaining.

Off-licence uses
1. RBD (zopiclone used in case studies)

Mechanism of action

As with benzodiazepines, the Z-drugs bind with high specificity to GABA-A ligand gated chloride channel complexes. On binding to these receptors they potentiate the action of GABA, increasing chloride conductance. The Z-drugs are thought to bind specifically to the $\alpha 1$ subunit whilst benzodiazepine drugs are less subunit selective. This is believed to account for their reduced anticonvulsant and anxiolytic activity compared to certain benzodiazepines.

Toxicity and side effects

- *Common—neurological*: anterograde amnesia, fatigue, headache and paraesthesiae. *Genitourinary*: dysmenorrhoea reported with zaleplon.
- *Serious—dermatological*: angio- oedema has been reported. *Psychiatric*: paradoxical reactions, ranging from mood disorders and nightmare to psychosis.

Contraindications

Absolute: Hypersensitivity to the Z-drug or its excipients, MG, sleep apnoea syndrome, severe respiratory and hepatic impairment. Zaleplon is also contraindicated in severe renal impairment.

Relative: Patients with a history of alcohol or substance abuse, chronic respiratory disease and depression.

In mild to moderate hepatic impairment, the maximum dose should be 5mg for zaleplon and zolpidem and 3.75mg zopiclone. In mild to moderate renal impairment patients should be monitored closely and lower doses used initially, as clearance may be reduced.

Uses in special populations

- *Elderly*: the elderly have an age- related deterioration in their renal and hepatic function, and are also more prone to adverse psychiatric 'paradoxical' reactions, e.g. agitation, confusion, and psychosis. They benefit from lower dosing regimens (Eszopiclone: starting dose of 1mg; usual maintenance dose of 1–2mg if difficulty getting to sleep is the primary problem. If difficulty staying asleep is the main problem, then 2mg can be used from the outset. Zaleplon: maximum dose is 5mg. Zolpidem: maximum dose is 6.25mg with extended release tablet, 5mg standard tablet and 1.75mg with the sublingual tablet. Zopiclone: the maximum dose is 3.75mg).
- *Pregnancy*: There are no controlled studies in humans. Animal studies suggest that eszopiclone results in increased rates of post-implantation loss and reduced birthweight, although this hasn't been demonstrated with other drugs of this class. The manufacturers advise against use in pregnancy. If they are used in pregnant mothers near term, then neonates should be monitored for side effects, including hypothermia, hypotonia, respiratory depression, and sedation.
- *Lactation*: Z-drugs are excreted into breast milk; hence the manufacturer advises against use in nursing mothers.

Efficacy

Zaleplon: As a result of its short duration of action is most effective at reducing sleep latency, with variable impact on total sleep duration. A randomised, double-blind study published in 1999 compared zaleplon with placebo. Sleep latency was reduced by 15–20 minutes vs. placebo. Further studies looking at memory, learning and psychomotor ability in healthy subjects administered zaleplon, zolpidem, triazolam or placebo at bedtime demonstrated that 10mg of zaleplon failed to impair any of this abilities even as soon as 1.25 hours post dose. Zolpidem and triazolam did impair these abilities.

Zolpidem: A randomised placebo-controlled trial of standard tablet zolpidem used for 35 nights at therapeutic doses demonstrated that zolpidem at 10mg resulted in a statistically significant improvement in sleep latency but had no significant impact on sleep maintenance. The modified release version of zolpidem has been shown in a further randomised, placebo-controlled trial to have the additional impact of significantly improving sleep maintenance when compared to placebo. Studies differ as to whether psychometric tests performed the day after treatment show impairment, it is likely subtle and more prominent in the elderly.

Zoplicone/Eszopiclone: A randomised, double-blind, placebo controlled trial of eszopiclone for the treatment of primary insomnia demonstrated that patients treated with high doses eszopiclone (3mg) reported improved sleep and daytime function compared to placebo ($P<0.001$). Insomnia severity index scores were reduced below clinically significant

levels in 50% of patients treated with eszopiclone vs 19% with placebo ($P<0.05$). Randomised controlled studies have compared zopiclone with benzodiazepine hypnotics including nitrazepam although none have compared it with the most commonly used dose of temazepam at 10mg, hence it is difficult to establish superiority between the benzodiazepines and Z-drugs for this indication. Night time dosing of both eszopiclone and zopiclone is associated with impaired performance in healthy adults the next morning in several psychometric tests. With regards the older adult where the impacts of zopiclone on cognitive impairment and psychomotor performance whilst on treatment are more pronounced CBT has been demonstrated to provide better short and longterm outcomes when compared to zopiclone. Sleep efficiency improved for 81.4 to 90.1% with CBT compared to a decrease from 82.3 to 81.9% with zopiclone according to polysomnographic studies.

Evidence for the use of zopiclone in the treatment of RBD is based on case study evidence, one case series demonstrated that 8 out of 11 patients with RBD found zopiclone effective in managing RBD symptoms. Compared to clonazepam the case series suggested there were less adverse events and episodes of treatment discontinuation because of side effects, which they attributed to the shorter half-life of zopiclone compared to clonazepam.

Dosing and monitoring

Zaleplon: Treatment is 10mg once at night. This should be for as short a period as possible and certainly for no longer than 2 weeks.

Zolpidem: Extended-release tablet: Treatment is 12.5mg once at night. Standard tablet: Treatment is 10mg once at night. Sublingual tablet: Treatment is 1.75mg for women and 3.5mg for men once at night. Treatment should be for as short a period as possible, usually between 3–14 days, and not exceeding 4 weeks including taper.

Zoplicone/Eszopiclone: Zopiclone: Usual dose is 7.5mg prior to bed (dosing regimen is the same in insomnia and RBD). Eszopiclone: Start treatment at 2mg prior to sleep, increase to 3mg if required. Treatment duration should not be longer than 4 weeks. For management of transient insomnia 2-5 days should be sufficient, short term insomnia 2-3 weeks.

Routine monitoring: Patients should be monitored for confusion, particularly the elderly and those with hepatic impairment.

Pharmacokinetics: See Table A.43

Table A.43 Pharmacokinetics of Z-drugs

	Eszopiclone	Zaleplon	Zolpidem (unmodified)	Zopiclone
Bioavailability	Not available	~30%	70%	>75%
Tmax	~1 hour	~1 hour	0.5-3 hours	1.5-2 hours
Protein Binding	~55%	~60%	~92.5%	~45%
Metabolism	Hepatic: CYP3A4, CYP2E1 and CYP2C8	Hepatic: Aldehyde oxidase > CYP3A4	Hepatic: CYP3A4, lesser degree CYP1A2	Hepatic: CYP3A4, CYP2E1 and CYP2C8
Pharmacologically active metabolites	Yes, weak	No	No	Yes, weak
Elimination half-life	~6 hours	~1 hour	2.4 hours	~5 hours
Excretion mechanism	~75% urinary (<10% as unchanged drug)	71% urine (<1% as unchanged drug)	56% urinary and 37% faeces as metabolites	~75% urinary (<10% as unchanged drug)

Interactions: See Table A.44

Food co-ingestion reduces oral bioavailabilty of zaleplon and zolpidem. Food also delays Tmax for eszopiclone and zolpidem but has no identified effect on zopiclone pharmacokinetics.

Table A.44 Interactions of Z-drugs

Medications which alter Z-drug plasma levels	Pharmacodynamic interactions
Levels decreased: CYP3A4 inducers e.g. carbamazepine and phenobarbital. **Levels increased:** CYP3A4 inhibitors e.g. cimetidine, erythromycin. Zaleplon only: Aldehyde oxidase inhibitors e.g. ondansetron, raloxifene and TCAs.	**With CNS depressants e.g. alcohol, anaesthetics, antihistamines, antipsychotics, opioids and TCAs:** Increased sedative side effects.

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3,4-diaminopyridine (amifampridine)

3,4-DAP was first used in clinical practice in the 1980s and is now the mainstay of symptomatic treatment for LEMS. Unlicensed preparations were widely used, before amifampridine phosphate (Firdapse®) was licensed in Europe in 2010. They differ from Firdapse® only by minor alterations in chemical structure and are still used in many regions where the cost of Firdapse® is considered prohibitive.

Uses

Licensed uses

In the UK

- *LEMS*: Firdapse® is licensed for symptomatic treatment in individuals aged 18 years and older.

No 3,4-DAP formulation is licensed in the USA.

Off-licence uses

- Congenital myasthenic syndrome and DBN.

Presentation

- *Trade name*: Firdapse®. Generic amifampridine is not widely available.
- *Formulation*: oral scored tablets, 10mg.

Mechanism of action

3,4-DAP prolongs presynaptic cell membrane depolarization by blockade of presynaptic voltage-gated potassium channels. This increases the influx of calcium into nerve endings and facilitates exocytosis of acetylcholine-containing vesicles. This action overcomes the effect of VGCC blockade in LEMS, resulting in successful neuromuscular transmission. In DBN, the same mechanism is believed to result in increased excitability of the Purkinje cells of the cerebellum, which may restore their inhibitory function on deep cerebellar and vestibular nuclei.

Toxicity and side effects

- *Common—cardiovascular*: arrhythmias, palpitations. *Gastrointestinal*: non-specific GI upset. *Neurological*: anxiety, blurred vision, chorea, dizziness, drowsiness, fatigue, headache, myoclonia, oral paraesthesiae, sleep disorders, weakness. *Respiratory*: exacerbation of asthma.

Contraindications

- *Absolute*: epilepsy (3,4-DAP lowers seizure threshold), uncontrolled asthma, and congenital long QT syndromes.
- *Relative*: in renal and hepatic impairment, the manufacturer recommends a smaller starting dose of 5–10mg and gradual uptitration.

Uses in special populations

- *Elderly*: no separate data on safety and efficacy in this group, but this group has an age-related decline in renal and hepatic function, and reduced doses may be required.

- *Pregnancy/lactation*: no safety data. The manufacturer advises avoidance and effective contraception for men and women during treatment with 3,4-DAP.

Efficacy

- *DBN*: a prospective, placebo-controlled study evaluated the effect of a single dose of 3,4-DAP (20mg) on DBN ($n = 17$, of various aetiologies). Mean peak slow-phase velocity was reduced from 7.2 (SD: 4.2) degrees/s before treatment to 3.1 (SD: 2.5) degrees/s 30min after treatment ($p < 0.001$). Subjects reported less oscillopsia and felt more stable, while standing and walking. Recently, 3,4-DAP (10mg) and 4-AP (10mg) were compared in a double-blind, prospective cross-over study ($n = 8$) for the treatment of DBN. 4-AP was shown to be more effective at 45 and 90min, as shown by significant reductions in slow-phase velocity.
- *LEMS*: four randomized, placebo-controlled trials of 3,4-DAP have been undertaken, showing an improvement on a validated myasthenia score of 2.44 points (95% CI 1.22–3.6) when measured between 3 and 8 days of treatment, and of CMAP amplitude by 1.36mV (95% CI 0.99–1.72) when compared with placebo. Clinical improvement lasts for up to 8 weeks.

Dosing and monitoring

Dosing

- *DBN*: as 3,4-DAP is an expensive drug, an observed test dose is often given first where patients are given either the medication or a placebo, and then the degree of nystagmus, gait, and dynamic visual acuity are assessed pre- and post-dosing. If the test dose is successful, then treatment can be started at 10mg od, and increased by 10mg every 1–2 weeks, as required/tolerated, up to 20mg tds.
- *LEMS*: 15mg od; 5mg increments every 4–5 days, up to a maximum of 60mg/day in 3–4 divided doses.

Monitoring Perform an ECG at baseline. Commonly, the first test dose is given, while the patient is attached to a cardiac monitor, to assess for the presence of arrhythmia.

Pharmacokinetics and interactions

Pharmacokinetics

Well-absorbed orally, with a bioavailability of 93–100%. Peak plasma concentration by 0.6–1.3h. Absorption is affected by food, with a 2-fold increase in T_{max}. Time to steady state has not been described in the manufacturer's literature. Metabolized to an inactive 3-*N*-acetylated metabolite. Half-life is around 2.5h. Amifampridine is fully renally excreted within 24h, 19% as the parent molecule and 81% as the metabolite.

Interactions See Table A.45.

Table A.45 Interactions of 3,4-DAP (amifampridine)

Pharmacodynamic interactions
With medications which prolong the QT interval, e.g. sultopride: risk of ventricular arrhythmias
With medications which reduce seizure threshold: increased risk of seizures

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Acetazolamide

Acetazolamide was first marketed in the UK as an AED in 1953. It can be used as a broad-spectrum AED (predominantly as an adjunct) and is also commonly used in the management of idiopathic intracranial hypertension. It benefits from a rapid onset of action and few pharmacological interactions. Its usefulness in epilepsy is limited by tolerance which can develop within 1–6 months of initiating therapy.

Uses

Licensed uses

In the UK

- *Epilepsy*: acetazolamide is licensed for treatment as an adjunct of atonic, atypical absence, myoclonic, tonic, and generalized tonic–clonic seizures in individuals of all ages.

Acetazolamide is not licensed for use in the treatment of epilepsy in the USA.

Off-licence uses

- Catamenial seizures, episodic ataxias, idiopathic intracranial hypertension, and periodic paralyses.

Presentation

- *Trade names*: Diamox® and Diamox® SR. Generics are available.
- *Formulations*: Diamox® is available as a modified-release capsule, a powder for reconstitution, IM or IV injection (as a sodium salt), and as a tablet. Modified-release capsule: 250mg. Powder for reconstitution: 500mg per vial. Tablet: 250mg.

Mechanism of action

- *Epilepsy*: acetazolamide is a carbonic anhydrase inhibitor. The exact mechanism of action in epilepsy is unclear. Its action may be mediated by inhibition of cerebral carbonic anhydrase enzymes or by systemic lowering of the pH, resulting in lowering of intracellular pH and suppression of neuronal activity. When used as an adjunct, a proportion of its effect may be due to increased tissue absorption of other AEDs such as phenytoin and phenobarbital.
- *Idiopathic intracranial hypertension*: acetazolamide is believed to reduce the formation of CSF by inhibiting the action of choroid plexus carbonic anhydrase activity.

Toxicity and side effects

Carbonic anhydrase inhibitors reduce intracellular pH, resulting in an increased incidence of hypokalaemia, metabolic acidosis, nephrolithiasis, paraesthesiae, polydipsia, and polyuria.

- *Common—dermatological*: allergic rash. *Endocrine*: reduced libido. *Gastrointestinal*: anorexia, diarrhoea, nausea, and parageusia. *Neurological*: dizziness, headache, and paraesthesiae.
- *Serious—dermatological*: Stevens–Johnson syndrome and toxic epidermal necrolysis have been reported. *Haematological*: rarely blood dyscrasias and bone marrow suppression.

Contraindications

- *Absolute*: pre-existing adrenocortical insufficiency due to its tendency for potassium loss, cirrhosis due to its predisposition for hyperammonaemia, pre-existing metabolic acidosis, and severe renal impairment. In addition, it should be avoided in patients treated with high-dose aspirin, as the combination has been reported to result in tachypnoea, loss of appetite, coma, and even death.
- *Relative*: the dose should be lowered in mild to moderate renal impairment (eGFR <60mL/min/1.73m^2). It should be used with caution in patients with hyponatraemia, hypokalaemia, a history of sulfonamide-induced allergic rash, and those with a previous history of nephrolithiasis or on treatments predisposing to stone formation, including topiramate and zonisamide. It should not be given to patients who are undergoing sustained treatment for chronic angle-closure glaucoma.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function, and benefit from lower dosing regimens. Co-prescription of other medications is also more likely in the elderly, and hence the risk of pharmacokinetic interactions is high.
- *Pregnancy*: some animal studies have demonstrated teratogenic effects; however, there are no controlled studies in humans. Use in pregnancy involves weighing up the potential benefits and side effects. Most would use alternative means of controlling CSF pressure in IIH, including weight control, regular lumbar puncture, or a neurosurgical procedure. The pharmacokinetics of acetazolamide during pregnancy have not been adequately studied.
- *Lactation*: acetazolamide is present in breast milk. Infant's plasma levels are 4–9% of maternal plasma levels, and this is thought to be too low to be harmful. If used, infants should be monitored for potential side effects. They should be switched to alternative methods of feeding if these are identified.

Efficacy

- *Epilepsy*: there is little good-quality evidence available as to the clinical efficacy of acetazolamide in epilepsy. What evidence there is comes from the 1950s and suggests that acetazolamide is a broad-spectrum AED, prone to the development of tolerance after 1–6 months. The tolerance is eliminated by intermittent use, making it useful if an AED is needed for short periods, e.g. catamenial epilepsy.
- *Idiopathic intracranial hypertension*: For discussion of the evidence base for use in IIH, please see the IIH section, pp. 14–5.

Dosing and monitoring

Dosing

- *Epilepsy*: the PO and IV dosages are between 0.25g and 1g daily in divided doses.
- *Idiopathic intracranial hypertension*: acetazolamide can be started at 250–500mg bd for BIH (or 15–25mg/kg/day in 2–3 divided doses), and increased according to response. Suggested dose increments are

15–25mg/kg at weekly intervals. Doses of up to 2–4g/day may be used. Side effects are dose-related, and higher doses may not be tolerated by some patients.

Routine monitoring Not recommended routinely. Serum bicarbonate can be monitored, if necessary.

Therapeutic drug monitoring Optimum seizure control occurs at plasma acetazolamide levels of 10–14mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

Acetazolamide has good oral absorption, with bioavailability >90%. It reaches maximum plasma concentrations (T_{max}) at 2–4h, and steady state in 2 days. It does not undergo hepatic metabolism. Hundred per cent of the dose is ultimately excreted unchanged by the kidneys. The half-life is 10–15h.

Interactions See Table A.46.

Table A.46 Interactions of acetazolamide

Medications whose plasma levels are altered by acetazolamide	Pharmacodynamic interactions
Levels increased: carbamazepine, ciclosporin, phenobarbital, and phenytoin	**With other carbonic anhydrase inhibitors and bicarbonate:** increased risk of nephrolithiasis
Levels decreased: lithium and primidone	**With high-dose aspirin:** risk of tachypnoea, anorexia, sedation, and even death

References

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Foldvary-Schaefer N, Falcone T. Catamenial epilepsy: pathophysiology, diagnosis and management. *Neurology* 2003;**61**(6 Suppl 2):S2–15.

Katayama F, Miura H, Takanashi S. Long-term effectiveness and side effects of acetazolamide in the treatment of refractory epilepsies. *Brain Dev* 2002;**24**(3):150–4.

Aciclovir

Aciclovir has been used in the management of herpes virus infections since the 1980s. It is most effective against HSV 1 and 2, to a lesser extent herpes zoster, and has only minimal effectiveness against CMV and EBV. It needs to be started without delay if herpes encephalitis is suspected, and continued for at least 2–3 weeks, potentially longer in the immunosuppressed.

Uses

Licensed uses

In the UK/USA

- *Viral encephalitis*: IV aciclovir is licensed for the treatment of herpes encephalitis in individuals of all ages. In the USA, the IV licence only includes herpes simplex encephalitis.

Off-licence uses

- None.

Presentation

- *Trade names*: Zovirax®. Generics are available.
- *Formulations*: aciclovir is available as multiple enteral and parenteral formulations. For the purposes of herpes encephalitis, only the IV form should be used. This is available as a powder for reconstitution and IV infusion and as a sterile concentrate. Powder for reconstitution and IV infusion: 250mg. Sterile concentrate: 10mL, 20mL, and 40mL at 25mg/mL.

Mechanism of action

Aciclovir is a purine nucleoside analogue. It specifically interacts with the viral thymidine kinase enzyme, leading to the creation of aciclovir triphosphate, a false substrate for viral DNA polymerase, which, when incorporated into a new DNA chain, results in termination, thereby preventing DNA replication.

Toxicity and side effects

- *Common—dermatological*: allergic rash, phlebitis with IV infusion, photosensitivity, pruritus, and urticaria. *Gastrointestinal*: abdominal pain, diarrhoea, nausea, reversible changes in hepatic enzymes, and vomiting. *Neurological*: fatigue and headache. *Renal*: deranged renal function.
- *Serious—dermatological*: severe local inflammatory reactions, potentially resulting in necrosis, may occur with tissue extravasation during IV infusion. Anaphylaxis and angio-oedema are rare. *Gastroenterological*: hepatitis. *Haematological*: anaemia, leucopenia, and thrombocytopenia have been reported. *Neurological*: severe neurological reactions, including ataxia, convulsions, tremors, and even coma can occur. *Psychiatric*: psychosis can occur. *Renal*: acute kidney injury, particularly with IV infusions—this can be minimized by slow IV infusions and ensuring adequate hydration.

Contraindications

- *Absolute*: hypersensitivity to aciclovir, its excipients, or valciclovir.
- *Relative*: use with caution in patients with underlying neurological abnormalities or previous neurological reactions to cytotoxic drugs, or who are co-prescribed IFN or intrathecal methotrexate, as these groups may be more prone to neurological side effects.

In renal impairment, the dose will need to be reduced.

- For the IV formulation: if CrCl is 25–50mL/min, give 5–10mg/kg bd, rather than tds; if CrCl is 10–25mL/min, give 5–10mg/kg od. Consult the product literature if CrCl is <10mL/min.
- For the oral formulation: if the eGFR is <10mL/min/1.73m^2, use the 800mg bd for herpes zoster infections; if the eGFR is 10–25mL/min/1.73m^2, use 800mg tds.

No dose adjustments are required in hepatic impairment, although it should be used with caution in severe impairment.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal function and may benefit from lower dosing regimens. The elderly are also more likely to get neuropsychiatric side effects and worsening renal function; hence urea and electrolytes (U&Es) should be frequently monitored.
- *Pregnancy*: limited data are available regarding the use of aciclovir in pregnancy. Small registries of human births and animal studies have not shown teratogenicity. However, aciclovir does cross the placenta, so the manufacturers advise against use, unless the benefits outweigh the risks.
- *Lactation*: aciclovir enters breast milk. The manufacturer advises against use by nursing mothers, unless the benefits outweigh the risks.

Efficacy

Compared to historic controls before the use of effective antivirals, aciclovir cuts the mortality rate from herpes simplex encephalitis by approximately two-thirds (from 70% to 20% case-based mortality). Increasing duration of symptoms prior to initiation of treatment is strongly associated with poorer outcome. Neurological sequelae occur in 70%, but these are of variable severity and functional impact. Approximately half of patients return to a normal life. For herpes zoster encephalitis, aciclovir is used on the basis of case study evidence and expert consensus; there are no controlled studies.

Dosing and monitoring

Dosing

For the treatment of herpes encephalitis, administer 10mg/kg tds for a minimum of 14–21 days for herpes simplex, and 14 days for herpes zoster. The need for ongoing treatment should be guided by the presence or absence of positive viral CSF PCR results, following a standard treatment course, and clinical response. Immunocompromised patients may need longer courses.

Routine monitoring Renal function, FBC, and liver function should be monitored frequently during treatment.

Pharmacokinetics and interactions

Pharmacokinetics

The terminal plasma half-life of aciclovir after IV infusion is ~3h; this can be prolonged to 20h in chronic renal failure. CSF levels reach 50% of corresponding plasma levels. Protein binding is 10–30%. Aciclovir is mainly eliminated via the renal tract, 75–80% as unchanged drug and 10–15% as the major metabolite 9-carboxymethoxymethylguanine.

Interactions See Table A.47.

Table A.47 Interactions of aciclovir

Medications whose plasma levels are altered by aciclovir	Medications whose plasma levels are altered by aciclovir	Pharmacodynamic interactions
Levels increased: cimetidine, mycophenolate mofetil (metabolite), probenecid, tenofovir, and theophylline	**Levels increased:** mycophenolate mofetil (metabolite)	**With nephrotoxics:** increased risk of acute kidney injury **With herpes zoster vaccine:** may diminish the effect of the vaccine

References

McGrath N, Anderson NE, Croxson M, *et al*. Herpes simplex encephalitis treated with aciclovir: diagnosis and long term outcome. *J Neurol Neurosurg Psychiatry* 1997;**63**(3):321–6.

Solomon T, Michael BD, Smith PE, *et al*. Management of suspected viral encephalitis in adults—Association of British Neurologists and British Infection Association National Guidelines. *J Infect* 2012;**64**(4):347–73.

Tunkel AR, Glaser CA, Bloch KC, *et al*. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2008;**47**(3):303–27.

Whitley RJ, Alford CA, Hirsch MS, *et al*. Vidarabine versus aciclovir therapy in herpes simplex encephalitis. *N Engl J Med* 1986;**314**(3):144–9.

Alemtuzumab

This drug, initially marketed as Campath®, was developed to treat B-cell chronic lymphocytic leukaemia. It was licensed for treatment of RRMS in the UK in 2014.

Uses

Licensed uses

In the UK/USA

- *MS*: alemtuzumab is licensed for the treatment of highly active RRMS in individuals aged 18 years and older.

Off-licence uses

- None.

Presentation

- *Trade name*: Lemtrada®. Generics are not available.
- *Formulation*: a concentrate for IV infusion (10mg/mL): 12mg.

Mechanism of action

Alemtuzumab is a humanized IgG1-kappa monoclonal antibody specific for the protein CD52 on the cell surface of B and T lymphocytes. It mediates cell lysis by complement fixation and cell-mediated cytotoxicity. This induces a prolonged depletion of circulating lymphocytes. B cells recover rapidly, but T cells can take up to 5 years to return to baseline levels.

Toxicity and side effects

- *Common—endocrine*: thyroid dysfunction. *Psychiatric*: anxiety and insomnia.
- *Serious—cardiovascular*: arrhythmia, cardiac failure, and MI. *Haematological*: anaemia, immune thrombocytopenic purpura (ITP), lymphopenia, and neutropenia. *Immunological*: ITP and thyroid dysfunction. Anaphylaxis infusion reactions (dyspnoea, fever, hypotension, rash, tachycardia, and urticaria) and opportunistic infections. *Renal*: autoimmune-related kidney disease, including anti-glomerular basement membrane disease. *Respiratory*: acute respiratory distress syndrome.

Contraindications

- *Absolute*: hypersensitivity to alemtuzumab (or murine proteins), active systemic infections, HIV, and active malignancy.
- *Relative*: the effects on patients with renal or hepatic impairment have not been studied, and caution is advised.

Use in special populations

- *Elderly*: alemtuzumab has not been studied in the elderly.
- *Pregnancy*: the teratogenicity of this drug is not known, but it is contraindicated in pregnancy. Active contraception should be used during, and for 6 months after, treatment.
- *Lactation*: breastfeeding should be avoided.

Efficacy

The *CARE-MS I* trial compared alemtuzumab 12mg/day to SC IFN-β-1a in patients who had not previously been treated with DMTs. The relapse rate over 2 years was 22% with alemtuzumab, compared to 40% with Interferon Beta-1a ($P<0.0001$). With no significant effect on 6-month disability progression. The *CARE-MS II* trial again compared alemtuzumab 12mg/day or 24mg/day to SC IFN-β-1a. The relapse rate over 2 years was 49% lower, compared to IFN, and the risk of 6-month sustained accumulation of disability was reduced by 42% ($p = 0.0098$).

Over a median 7-year follow-up, most (52%) patients received just two cycles; 36% required three cycles, 8% four, and 1% five. Disease stabilization was seen in the majority of patients, with 67.8% showing improved or unchanged 6-month sustained disability, compared with baseline, and 59.8% showing overall improvement or stabilization of disability using an area under the curve analysis. Secondary autoimmunity was the most frequently observed side effect, occurring in 47.7% patients, commonly involving the thyroid gland.

Dosing and monitoring

Dosing

IV infusion of 12mg each day for 5 consecutive days, followed by 12mg each day for 3 days after 1 year.

Routine monitoring

Patients should be pre-treated with corticosteroids (1g methylprednisolone for the first 3 days of the treatment course), antihistamines, and oral aciclovir (200mg bd for 1 month) to prevent herpes zoster infections. Patients should be observed for infusion reactions, which can be severe. Prophylaxis against *Pneumocystis jiroveci* pneumonia (PCP) is used for a minimum of 2 months and until the CD4 count exceeds 200×10^6/L. There is a significant risk of thrombocytopenia and neutropenia during treatment. FBC should be measured before, and at regular intervals (current recommendation is monthly) during, treatment. If platelet counts fall below 25×10^9/L or neutrophil counts fall below 0.25×10^9/L, alemtuzumab should be withheld. The drug should be permanently discontinued if autoimmune thrombocytopenia or anaemia develops. Thyroid function tests (TFTs) and urinalysis should also be monitored regularly during treatment.

Pharmacokinetics and interactions

Pharmacokinetics

Clearance decreases with repeated doses, due to the reducing numbers of CD52 receptors in the periphery. With accumulation in the plasma, the rate of elimination reaches zero-order kinetics. The half-life is 8h following the initial dose and increases up to 6 days after repeated doses.

Interactions Patients should only ever receive irradiated blood products following treatment, due to the risk of transfusion-associated graft-versus-host disease. Patients should not receive live vaccines for 12 months following treatment.

References

Cohen JA, Coles AJ, Arnold DL, *et al*; CARE-MS I investigators. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012;**380**(9856):1819–28.

Coles AJ, Fox E, Vladic A, *et al*; Alemtuzumab more effective than interferon beta-1-a at 5 year follow up of CAMMS223 clinical trial. *Neurology* 2012;**78**(14):1069–78.

Coles AJ, Twyman CL, Arnold DL, *et al*; CARE-MS II investigators. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomized controlled phase 3 trial. *Lancet* 2012;**380**(9856):1829–39.

Tuohy O, Costelloe L, Hill-Cawthorne D, *et al*. Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy. *J Neurol Neurosurg Psychiatry* 2015;**86**(2):208–15.

Alteplase

Alteplase is a parenteral fibrinolytic agent, which is the only agent of its class to be licensed in the management of acute ischaemic stroke. It was first approved for acute ischaemic stroke in the UK in the late 1990s. Fibrinolytic therapy has the potential to restore cerebral blood flow and markedly improve neurological outcome when used in the first hours post-acute ischaemic stroke.

Uses

Licensed uses

In the UK/USA

Alteplase is licensed for the treatment of acute ischaemic stroke if treatment is within 4.5h of symptom onset (USA: 3h after symptom onset), and intracranial haemorrhage is excluded by imaging, in individuals aged 18 years and older.

Off-licence uses

- None.

Presentation

- *Trade name*: Actilyse®. Generics are not available.
- *Formulations*: alteplase is available as a powder for reconstitution and injection or infusion in 10mg, 20mg, and 50mg vials.

Mechanism of action

Alteplase is a tissue plasminogen activator (t-PA) which converts plasminogen to plasmin. Plasmin is an enzyme that degrades fibrin clots. The aim is to reduce the impact of ischaemia by restoring blood flow through the occluded artery.

Toxicity and side effects

- *Common—cardiovascular*: hypotension. *Gastrointestinal*: nausea and vomiting. *Haematological*: iron deficiency anaemia. *Immunological*: allergic reaction, injection site reaction.
- *Serious—cardiovascular*: recurrent ischaemia or angina, heart failure, reperfusion arrhythmias. *Gastrointestinal*: haemorrhage (occasionally major). *Neurological*: intracranial haemorrhage. *Respiratory*: pulmonary oedema.

Contraindications

- *Absolute*: alteplase is contraindicated in cases where there is a high risk of haemorrhage; according to the product licence, this includes:
  1. significant bleeding at any time within the past 6 months;
  2. known haemorrhagic diathesis;
  3. patients receiving effective oral anticoagulant treatment;
  4. known history of, or suspected, intracranial/subarachnnoid haemorrhage;
  5. any history of CNS damage, e.g. neoplasm, aneurysm, surgery;

6. traumatic external heart massage, obstetric delivery, puncture of a non-compressible blood vessel (e.g. subclavian or jugular vein) within the last 10 days;
7. elevated BP—systolic >185mmHg or diastolic >110mmHg;
8. bacterial endocarditis or pericarditis;
9. acute pancreatitis;
10. ulcerative gastrointestinal disease during the last 3 months, oesophageal varices, arterial aneurysm, or arterial/venous malformations;
11. neoplasm with increased bleeding risk;
12. severe liver disease, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices), and active hepatitis;
13. major surgery or significant trauma within the past 3 months;
14. CT evidence of multilobar infarction;
15. blood glucose <2.7mmol/L or >22.2mmol/L (<50 or >400mg/day);
16. platelet count <100 000/mm^3.

In the USA, the American Stroke Association recommends additional contraindications to alteplase use in the management of acute stroke when considered 3–4.5h post-onset of symptoms:

1. age >80 years;
2. patients taking oral anticoagulants (irrespective of INR);
3. a baseline National Institutes of Health Stroke Scale (NIHSS) score of >25;
4. ischaemic injury occupying more than one-third of the MCA territory;
5. patients with both a prior stroke and diabetes.

In the experienced stroke physician's hands, some of the contraindications listed may not be absolute in practice, and, in complex cases, careful consideration of the balance of risk and benefit is required.

- *Relative*:
  1. seizures at onset of stroke with post-ictal residual neurological impairments;
  2. pregnancy;
  3. minor or rapidly improving stroke symptoms;
  4. acute MI within the previous 3 months.

Uses in special populations

- *Elderly*: in the elderly, no dose adjustment is required. However, the benefits of therapy should be carefully weighed up against the risk of adverse events such as bleeding.
- *Pregnancy*: should be used with caution and only if benefits outweigh risks. Its use may lead to premature separation of the placenta in the first 18 weeks of pregnancy. It additionally confers an increased risk of maternal haemorrhage throughout pregnancy and post-partum, while also having the theoretical risk of fetal haemorrhage throughout pregnancy.
- *Lactation*: there are no data available, and hence it should be used with caution.

Efficacy

Early trials of alteplase use within the first 3h post-symptom onset in acute ischaemic stroke showed that patients were at least 30% more likely to have minimal or no disability at 3 months, when compared to placebo (*NINDSr-tPA*). The *ECASS III* RCT suggested that favourable outcomes could be obtained when alteplase was used up to 4.5h post-symptom onset. However, other similar small studies suggested there was no benefit in giving alteplase after 3h (*ATLANTIS* and *ECASS II*).

Ultimately, a much larger study the *IST-3* trial was run to clarify whether alteplase should be used in situations where benefit was uncertain, e.g. >3h from onset, >80 years. It was a large (n = 3035, of whom 1617 were older than 80 years of age) randomized, open-label trial, which ascertained that patients thrombolysed within 6h of symptom onset had improved functional outcomes, a benefit that extended to the population aged >80. However, no benefit was conferred with regard to mortality.Those who were thrombolysed faced an increased number of deaths within the first 7 days (7% vs 1%), while those who were not had a higher mortality rate between 7 days and 6 months.

Dosing and monitoring

Dosing

The total dose is 900 micrograms/kg (maximum 90mg). The first 10% of the dose is given by IV injection over 60s, then the remainder by IV infusion over 60min.

Monitoring It is recommended that, when alteplase is administered, standard resuscitation equipment should be available. Due to an increased haemorrhagic risk, antiplatelet agents should not be started until 24h after administration of alteplase.

Pharmacokinetics and interactions

Pharmacokinetics

When administered IV, alteplase is inactive in the circulatory system, until it binds to the fibrin clot where it is subsequently activated, inducing the conversion of plasminogen to plasmin and leading to the dissolution of the fibrin clot. Alteplase is cleared rapidly from the circulating blood and metabolized mainly by the liver, with a half-life of ~5min. Fibrinolytic activity is present for a further hour following cessation of the infusion.

Interactions See Table A.48.

Table A.48 Interactions of alteplase

Pharmacodynamic interactions
With abciximab, aspirin, clopidogrel, heparin, NSAIDs, ticlopidine, vitamin K antagonists, warfarin: increased risk of bleeding **With ACE inhibitors:** increased risk of angio-oedema

References

Hacke W, Kaste M, Bluhmki E, *et al*. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;**359**(13):1317–29.

Sandercock P, Wardlaw JM, Lindley RJ, *et al*. (2012). The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet* 2012;**379**(9834):2352–63.

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Wechsler LR. Intravenous thrombolytic therapy for acute ischemic stroke. *N Engl J Med* 2011;**364**(22):2138–214.

Amantadine

Amantadine was first marketed in the 1960s for the treatment of influenza. It was serendipitously found to have a beneficial effect on the symptoms of PD in patients treated for influenza in 1968. It can be used as monotherapy or as an adjunct to levodopa, particularly in those with troublesome dyskinesias.

Uses

Licensed uses

In the UK/USA

- *PD*: amantadine is licensed for the treatment of PD in individuals aged 10 years and older in the UK, and 1 year and older in the USA.

In the USA

- *Drug-induced extrapyramidal syndrome*: amantadine is also licensed for the treatment of drug-induced extrapyramidal side effects in individuals aged 1 year and older.

Off-licence uses

- Chorea and MS-related fatigue.

Presentation

- *Trade names*: Lysovir® and Symmetrel®. Generics are available.
- *Formulations*: amantadine is available as a capsule and a syrup. Capsule: 100mg. Syrup: 50mg/5mL in a 150mL bottle.

Mechanism of action

The exact mechanism of action in the treatment of PD is unknown; proposed mechanisms include: inhibition of dopamine reuptake and enhanced dopamine release at the presynaptic membrane, post-synaptic upregulation of D2 receptors, antimuscarinic activity, and non-competitive NMDA receptor antagonism (NMDA receptor blockade has been shown to reduce the severity of levodopa-induced dyskinesias in monkey models of PD).

Toxicity and side effects

- *Common—cardiovascular*: orthostatic hypotension and peripheral oedema. *Dermatological*: livedo reticularis. *Gastrointestinal*: anorexia, constipation, diarrhoea, dry mouth, and nausea. *Neurological*: ataxia, dizziness, dream abnormality, fatigue, headache, insomnia, somnolence. *Psychiatric*: agitation, anxiety, confusion, delirium, depression, and hallucinations.
- *Serious—haematological*: agranulocytosis. *Neurological*: lowered seizure threshold and NMS (related to dosage reduction or sudden withdrawal). *Ophthalmological*: corneal oedema. *Psychiatric*: mania, psychosis, and suicide.

Contraindications

- *Absolute*: known hypersensitivity to amantadine, severe renal impairment (CrCl <15mL/min).
- *Relative*: use with caution in angle-closure glaucoma, underlying neuropsychiatric disorders, cardiovascular disorders, and known seizure disorder (lowers seizure threshold). No dose alteration in hepatic impairment. In renal impairment, reduce the dose to 100mg every 2–3 days if CrCl is 15–35mL/min.

Uses in special populations

- *Elderly*: the elderly experience an age-related reduction in renal function and are more prone to side effects, including orthostatic hypotension; hence a lower dosing regimen may be appropriate.
- *Pregnancy*: teratogenicity noted in animal studies and case reports in humans; use in pregnancy is contraindicated.
- *Lactation*: amantadine is present in milk; its manufacturers advise avoidance in nursing mothers.

Efficacy

A randomized, placebo-controlled trial of amantadine (300mg/day) was conducted in advanced PD patients with motor fluctuations and dyskinesias treated with levodopa. Amantadine treatment was superior to placebo in suppressing dyskinesias, with an average duration of effect of 4.9 vs 1.3 months with placebo (p <0.001). There was an increase in 'on' time and a decrease in 'off' time; however, neither was significant. Another placebo-controlled study of 17 patients treated with amantadine found the anti-dyskinetic effect to be maintained at 1 year.

Dosing and monitoring

Dosing

Start treatment at 100mg od, and increase to 100mg bd at 1 week. This is the usual maintenance dose, although amantadine can be further uptitrated by 100mg a week to a maximum dose of 400mg/day, if required. Onset of effect may be seen after 1–2 days but often is lost after a few months. Avoid giving the second dose in the evening, due to risk of insomnia.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is 66–100%. T_{max} is 3–4h. Steady state is reached at 3 days. Sixty-seven per cent is protein-bound (plasma proteins and red blood cells). Amantadine undergoes minimal metabolism by *N*-acetylation. The elimination half-life is 90%; the predominant mechanism is renal secretion, ~90% as unchanged drug.

Interactions See Table A.49.

Table A.49 Interactions of amantadine

Medications which alter amantadine plasma levels	Pharmacodynamic interactions
Levels increased: drugs which impair renal clearance (e.g. thiazide diuretics, and trimethoprim)	**With anticholinergics:** can enhance the anticholinergic effects of amantadine **With CNS depressants, e.g. alcohol:** may increase CNS toxicity

References

Fox S, Katzenschlager R, Lim S, *et al*. The Movement Disorder Society Evidence-Based Medicine Review Update: treatments for the motor symptoms of Parkinson's disease. *Mov Disord* 2011;**26**(Suppl 3):S2–41.

Metman L, Del Dotto P, LePoole K, Konitsiotis S, Fang J, Chase TN. Amantadine for levodopa-induced dyskinesias: a 1-year follow-up study. *Arch Neurol* 1999;**56**(11):1383–6.

Thomas A, Iacono D, Luciano AL, Armellino K, Di Iorio A, Onofrj M. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2004;**75**(1):141–3.

Ammonium tetrathiomolybdate

Ammonium tetrathiomolybdate, an unlicensed agent previously used to treat copper toxicosis in animals, is emerging as a potential new chelating treatment in WD. Its improved side effect profile, in particular the reduced incidence of neurological deterioration on initiation of treatment (compared to the existing chelating therapies available for WD) and the encouraging results from short-term clinical efficacy studies have promoted its off-licence use.

Uses

Licensed uses

In the UK/USA

- Ammonium tetrathiomolybdate has no licensed uses.

Off-licence uses

- WD.

Presentation

- *Trade names*: it is not yet commercially available.
- *Formulations*: in clinical trials, it has been given via the oral route.

Mechanism of action

Ammonium tetrathiomolybdate acts to reduce total body copper in two ways; firstly, it binds copper from both food and endogenously secreted intestinal copper, to form a complex which prevents intestinal copper absorption. Secondly, when absorbed, tetrathiomolybdate complexes available copper with albumin, thereby preventing cellular absorption and increasing systemic copper removal.

Toxicity and side effects

- *Common—gastrointestinal/hepatic*: a mild elevation of aminotransferase enzymes has been observed in some clinical studies (~5% of patients). This effect occurs much less frequently if the daily dose does not exceed 120mg and is quickly responsive to a drug holiday and/or dose reduction.
- *Serious—haematological*: the predominant adverse effect observed in clinical studies is mild bone marrow suppression, producing anaemia, leucopenia, and occasionally thrombocytopenia. This is probably because the bone marrow requires copper for cellular proliferation. It is a dose-related effect; it occurs much less frequently if the daily dose does not exceed 120mg and is quickly responsive to a drug holiday and/or dose reduction. *Neurological*: deterioration of the neurological manifestations of WD occurs in ~4%, i.e. a lower rate than with alternative copper-chelating agents.

Contraindications

- *Absolute*: hypersensitivity to ammonium tetrathiomolybdate.
- *Relative*: studies have not been performed in patients with hepatic or renal impairment; hence no guidance with regard to dose adjustment can be recommended—use with caution.

Uses in special populations

- *Elderly/pregnancy/lactation*: there are no data on the safety and efficacy of tetrathiomolybdate in patients above 65 years of age, those who are pregnant, or nursing mothers; use with caution.

Efficacy

An open-label study of 55 patients presenting with neurological symptoms of WD treated with tetrathiomolybdate showed that the neurological symptoms worsened in only 4% of patients (two of 55) during the 8 weeks of tetrathiomolybdate treatment, as indicated by serial quantitative neurology and speech scores.

When comparing tetrathiomolybdate with trientine, a double-blind RCT of 48 patients with neurological symptoms of WD demonstrated that deterioration of these neurological symptoms occurred in only 4% of patients (one of 25), compared to 26% in the trientine arm ($p < 0.05$). Furthermore, at a 3-year period, patients initially treated with tetrathiomolybdate recovered an average of 81% of their neurological function.

Dosing and monitoring

Dosing

In the RCT by Brewer and colleagues, patients received tetrathiomolybdate in doses of 20mg tds with meals and 20mg tds in between meals.

Routine monitoring Regular monitoring of the FBC and liver profile should be undertaken.

Pharmacokinetics and interactions

Pharmacokinetics

- Pharmacokinetic studies have not been carried out.

Interactions

- None as yet reported.

References

Brewer GJ, Askari F, Lorincz MT, *et al*. Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease. *Arch Neurol* 2006;**63**(4):521–7.

Brewer GJ, Hadera P, Kluin KJ, *et al*. Treatment of Wilson disease with ammonium tetrathiomolybdate: III. Initial therapy in a total of 55 neurologically affected patients and follow-up with zinc therapy. *Arch Neurol* 2003;**60**(3):379–85.

Apixaban

Apixaban was first marketed in the UK in 2012. It is an effective anticoagulant, which can be used when there is poor INR control despite compliance with warfarin therapy, or in patients who are allergic to, or unable to tolerate, warfarin.

Uses

Licensed uses

In the UK/USA

- *Prevention of stroke*: apixaban is licensed for the prophylaxis of stroke and systemic embolism in patients with non-valvular atrial fibrillation in individuals aged 18 years and older. In the UK, patients need to score at least 1 point on the CHADS2 VASc score.

Off-licence uses

- None.

Presentation

- *Trade name*: Eliquis®. Generics are not available.
- *Formulations*: apixaban is available as a 2.5mg tablet.

Mechanism of action

Apixaban is a potent, oral, reversible, direct, and highly selective active site inhibitor of factor Xa. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development. Apixaban has no direct effects on platelet aggregation but indirectly inhibits platelet aggregation induced by thrombin.

Toxicity and side effects

- *Common—dermatological*: bruising. *Gastrointestinal*: nausea. *Haematological*: anaemia.
- *Serious—gastrointestinal*: intra-abdominal haemorrhage. *Haematological*: haemorrhage. *Neurological*: ICH.

Contraindications

- *Absolute*: hypersensitivity to apixaban or its excipients. Active bleeding, conditions associated with an increased risk of bleeding, e.g. peptic ulcer disease, ICH, etc. Severe hepatic impairment or any degree of hepatic disease with coagulopathy and a risk of bleeding. Severe renal impairment: CrCl <15mL/min. *Metallic heart valves (apixaban has not been trialled in this setting)*.
- *Relative*: in those with CrCl from 15 to 29mL/min and lesser degrees of hepatic impairment, apixaban should be used with caution.

Uses in special populations

- *Elderly*: dose adjustment may be necessary in the elderly population. The elderly experience an age-related decline in hepatic and renal function; hence these parameters should be regularly monitored, while on treatment.

- *Pregnancy*: should only be used if the benefit outweighs the potential increased risk of bleeding
- *Lactation*: avoid in those who are breastfeeding—animal studies have demonstrated that it is excreted at high levels in breast milk.

Efficacy

In the *ARISTOTLE* trial, 18 201 AF patients with intermediate risk of clinical thromboembolic stroke (mean CHADS2 score of 2.1) were randomly assigned to either *apixaban* (5mg bd) or *warfarin* (target INR 2.0–3.0). The primary composite endpoint of stroke and systemic embolism was significantly reduced (0.33% per year) in the apixaban group. The hazard ratio with apixaban was 0.79 (95% CI 0.66–0.95; p <0.001 for non-inferiority and p = 0.01 for superiority).

Dosing and monitoring

Dosing

For the prevention of stroke in non-valvular AF, the recommended dose is 5mg bd. Halve the dose to 2.5mg bd if two or more of age >80 years, body weight <60kg, or serum creatinine ≥133micromol/L are present.

Monitoring

There is no need for monitoring of coagulation parameters during treatment with apixaban in routine clinical practice. However, if clinically indicated, the Rotachrom® anti-FXa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g. overdose and emergency surgery.

Pharmacokinetics and interactions

Pharmacokinetics

The absolute bioavailability of apixaban is ~50% for doses up to 10mg. T_{max} occurs at 3–4h after dosing. Apixaban demonstrates linear pharmacokinetics, with dose-proportional increases in exposure for oral doses up to 10mg. It is predominantly metabolized by CYP3A4, but CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2J2 play minor roles in its metabolism. Apixaban is also a substrate for the p-glycoprotein transport protein. It has multiple routes of elimination; ~25% is recovered as metabolites, with the majority recovered in faeces. Renal excretion of apixaban accounts for ~27% of total clearance. Apixaban has a half-life of ~12h.

Interactions See Table A.50.

Table A.50 Interactions of apixaban

Medications which alter apixaban plasma levels	Pharmacodynamic interactions
Levels decreased: rifampacin **Levels increased:** HIV protease inhibitors, e.g. indinavir, and azole antifungals, e.g. itraconazole and ketoconazole	**With anticoagulants, antiplatelets, IV diclofenac, and sulfinpyrazone:** increased risk of bleeding

References

Easton JD, Lopes RD, Bahit MC, *et al*. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. *Lancet Neurol* 2012;**11**(6):503–11.

Granger CB, Alexander JH, McMurray JV, *et al*. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**(11):981–92.

Aspirin

Aspirin is a salicylic ester of acetic acid. It has a wide range of clinical uses, owing to its analgesic, antipyretic, anti-inflammatory, and antithrombotic properties. It was first marketed in the UK in 1939.

Uses

Licensed uses

In the UK

- Cerebrovascular disease: aspirin is licensed for the secondary prevention of thrombotic cerebrovascular disease in individuals aged 16 years and older.

In the USA

- Cerebrovascular disease: aspirin is licensed for the prevention and treatment of acute stroke and TIA in individuals aged 12 years and older.

Off-licence uses

- Prevention of stroke in patients with AF, treatment of thrombotic complications of neuro-Behçet's and SLE, and treatment of cortical venous sinus thrombosis.

Presentation

Aspirin is available in combination with multiple other agents, including caffeine, codeine, and dipyridamole. Only formulations containing aspirin alone are discussed further.

- *Trade names*: Disprin®, Nu-Seals®, and Resprin®.Generics are available.
- *Formulations*: aspirin is available as a dispersible tablet, enteric-coated tablet, standard tablet, and suppository. Tablets: 75mg, 81mg (USA), 300mg, 325mg (USA), 500mg (USA), and 650mg (USA) doses. Suppository: 300mg and 600mg.

Mechanism of action

Aspirin irreversibly inhibits COX enzymes. This reduces the formation of the pro-aggregatory molecule thromboxane A2 by platelets, thus reducing the rate of further clot formation.

Toxicity and side effects

- *Common—gastrointestinal*: gastrointestinal irritation. *Haematological*: iron deficiency anaemia. *Immunological*: allergic reaction. *Neurological*: tinnitus. *Respiratory*: bronchospasm.
- *Serious—gastrointestinal*: major haemorrhage. *Immunological*: angio-oedema.

Contraindications

- *Absolute*: active peptic ulceration, haemophilia and other bleeding disorders, pregnancy (third trimester), gout, severe hepatic impairment. History of hypersensitivity to aspirin or any other NSAID which includes attacks of asthma, angio-oedema, urticardia, or rhinitis. Severe renal (CrCl <10mL/min) and severe hepatic impairment.

- *Relative*: concurrent use of NSAIDs or anticoagulants, poorly controlled hypertension (increased risk of intracranial bleeding), in those aged <21 due to increased risk of Reye's syndrome. Use with caution in mild to moderate renal impairment, as it can cause further deterioration in renal function, and the risk of gastrointestinal bleed may be increased.

Uses in special populations

- *Elderly*: use with caution, as the elderly are at an increased risk of gastrointestinal bleeding.
- *Pregnancy*: aspirin is associated with anaemia and intrauterine growth retardation, and may increase fetal mortality. It should be used only if benefits outweigh the risk and ideally stopped in the third trimester to reduce the risk of bleeding during delivery.
- *Lactation*: aspirin is present in breast milk and should be avoided due to the possible risk of Reye's syndrome to an infant.

Efficacy

Most national guidelines recommend the acute treatment of stroke with aspirin as soon as possible after brain imaging has excluded haemorrhage. Systematic reviews of large trials (CAST, IST) have clearly established that starting aspirin therapy within the first 48h of acute ischaemic stroke avoids death or disability at 6 months for ~10 per 1000 patients treated. The benefit of aspirin is not dependent on aspirin dosages, although maximal thromboxane inhibition may only be achieved at high doses; hence current practice in the UK is to load aspirin for 2 weeks at 300mg following an acute stroke, then to switch to clopidogrel or drop the aspirin dose to 75mg to reduce the risk of gastric side effects.

Dosing and monitoring

Dosing

In acute stroke, use 300mg of aspirin od for 2 weeks. For prevention of strokes (including secondary to AF), use 75mg od long-term. Proton pump inhibitors may be commenced, in addition to aspirin, if dyspepsia is reported. If the patient has dysphagia, use an enteral tube or a suppository.

Monitoring

FBC and renal function monitoring should be performed regularly in patients at risk of bleeding or renal impairment, respectively.

Pharmacokinetics and interactions

Pharmacokinetics

Aspirin is largely absorbed in the small intestines; a small amount of the ionized form is absorbed by the stomach. Bioavailability is 50–75%. T_{max} is 1–2h. Aspirin is rapidly hydrolysed to salicylate predominantly by the gastrointestinal mucosa and red blood cells. 50–80% of salicylate is bound to plasma proteins. It is predominantly metabolized hepatically by conjugation with glycine. The half-life of salicylate is 3h at doses of 300mg—this increases markedly at higher doses. Excretion is predominantly renal—75% as salicyluric acid.

Interactions See Table A.51.

Table A.51 Interactions of aspirin

Medications which alter aspirin plasma levels	Medications whose plasma levels are altered by aspirin	Pharmacodynamic interactions
Levels decreased: corticosteroids and kaolin	**Levels increased:** methotrexate and zafirlukast	**With acetazolamide:** increased risk of toxicity with high-dose aspirin
Levels increased: metoclopramide		**With clopidogrel, corticosteroids, coumarins, iloprost, NSAIDs, SSRIs, and venlafaxine:** increased risk of bleeding
		Probenecid, spironolactone, sulfinpyrazole: aspirin antagonizes their effects
		With valproate and phenytoin: aspirin enhances their effects
		Varicella-zoster vaccines: possible increased risk of Reye's syndrome

References

CAST (Chinese Acute Stroke Trial) Collaborative. CAST: randomised placebo-controlled trial of early aspirin use in 20 000 patients with acute ischemic stroke. *Lancet* 1997;**349**(9066):1641–9.

Chen Z, Sandercock P, Pan HC, *et al*. Indications for early aspirin use in acute ischemic stroke: A combined analysis of 40 000 randomized patients from the chinese acute stroke trial and the international stroke trial. On behalf of the CAST and IST collaborative groups. *Stroke* 2000;**31**(6):1240–9.

International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both or neither among 19435 patients with acute ischemic stroke. *Lancet* 1997;**349**(9065):1569–81.

Sandercock P, Gubitz G, Foley P, *et al*. Antiplatelet therapy for acute ischaemic stroke. *Cochrane Database Syst Rev* 2008;**3**:CD000029.

Azathioprine

Azathioprine was developed in the 1950s as a chemotherapeutic agent and was subsequently used in the 1960s as one of the early immunosuppressants for transplantation. It is currently used in a wide range of autoimmune neurological diseases.

Uses

Azathioprine is usually indicated in immunosuppressive regimens as an adjunct to basic immunosuppression with corticosteroids, which form the mainstay of therapy. It may also be used in patients who are intolerant to corticosteroids. Common neurological uses are given below:

- autoimmune limbic encephalitis;
- Behçet's (first-line, chronic);
- GCA (second-line, chronic);
- IBM;
- LEMS (first-line, chronic);
- MG (first-line, chronic);
- neurolupus (first-line, chronic);
- NMO (first-line, chronic);
- PM/DM (first-line, chronic);
- Sjögren's syndrome (first-line, chronic);
- Susac's syndrome;
- vasculitis.

Presentation

- *Trade names*: Azamune®, Azasan®, and Imuran®. Generics are available.
- *Formulations*: azathioprine is available as oral tablets (Azamune® and Azasan®) and vials of powder for IV infusion (Imuran®). Oral tablet: 25, 50, 75, and 100mg. Vial: 50mg.

Mechanism of action

Azathioprine is metabolized into 6-mercaptopurine, which acts both as a purine antimetabolite inhibiting nucleic acid synthesis and as an alkylating agent. This allows the drug to modulate immunological responses by limiting leucocyte proliferation. It also exhibits antineoplastic effects.

Toxicity and side effects

The principal side effect is a dose-related suppression of bone marrow function.

- *Common—gastrointestinal*: nausea and vomiting. *Haematological*: anaemia, leucopenia, and thrombocytopenia. *Immunological*: increased risk of infection.
- *Serious—dermatological*: Kaposi's sarcoma, squamous cell carcinoma, and Stevens–Johnson syndrome. *Gastrointestinal*: gastric ulceration, hepatic impairment (including veno-occlusive disease), and pancreatitis. *Gynaecological*: cervical and vulval cancer. *Haematological*: acute myeloid leukaemia, bone marrow failure, myelodysplastic syndromes, and non-Hodgkin's lymphoma. *Immunological*: hypersensitivity reactions (including acute kidney injury, anaphylaxis, and vasculitis). *Respiratory*: interstitial pneumonitis (reversible).

Contraindications

- *Absolute*: hypersensitivity, severe infections, severe hepatic impairment, bone marrow failure, pancreatitis, and concurrent live vaccination.
- *Relative*: patients with renal disease or mild to moderate hepatic impairment should be given doses at the lower end of the normal range.

Use in special populations

- *Elderly*: this drug has not been studied in the elderly; however, the elderly experience an age-related decline in hepatic and renal function and should be given doses at the lower end of the normal range.
- *Pregnancy*: azathioprine is teratogenic in animals and should be avoided, where possible, in pregnancy.
- *Lactation*: breastfeeding is contraindicated.

Efficacy

See under separate conditions in the relevant chapters.

Dosing and monitoring

Dosing

An oral dose of 1–3mg/kg daily is typically used in autoimmune conditions. A usual starting dose is between 25 and 50mg/day. This should be taken with meals. The dose is then gradually increased over weeks, with close monitoring, to achieve optimum symptomatic control (usually around 150mg/day).

Routine monitoring

Thiopurine methyltransferase (TPMT) metabolizes azathioprine and has reduced enzyme activity in up to 10% of the population. TMPT levels should be measured in all patients prior to treatment initiation. Regular FBC monitoring is required during treatment. This should be weekly for the first 2 months and can then be done at least every 3 months thereafter. Patients should be advised to seek help if they develop a fever, sore throat, bruising, bleeding, or signs of infection. They should also be warned about the increased risk of skin cancer, and the skin should be examined at regular intervals. Withdrawal of this drug can lead to severe relapses in disease and should be done gradually. Chickenpox can be fatal in the immunocompromised, and patients should be advised to seek medical help if they are not immune and become exposed.

Pharmacokinetics and interactions

Pharmacokinetics

The bioavailability of azathioprine is highly variable: 30–90%. Plasma levels peak within 2h of administration. The drug is rapidly distributed, with a maximum of 30% binding to plasma proteins. Azathioprine is a prodrug; it is metabolized by both the liver and kidneys to the principal active metabolite 6-mercaptopurine. The plasma half-life of azathioprine is 30–80min, and that of 6-mercaptopurine 3–5h. 6-mercaptopurine is subsequently metabolized by several different enzymes, including TMPT and xanthine oxidase, into inactive metabolites. Around 50% of a given dose is excreted in the urine in the first 24h, and 12.6% can be found in the stool at 48h. Only a small amount of <2% is excreted as unchanged drug.

Interactions See Table A.52.

Table A.52 Interactions of azathioprine

Medications which alter azathioprine plasma levels	Medications whose plasma levels are altered by azathioprine	Pharmacodynamic interactions
Increased levels: allopurinol	Decreased levels: warfarin	With ACE inhibitors, aminosalicylates, NSAIDs, ribavirin, sulfamethoxazole, and trimethoprim: the myelosuppressive effects are increased With febuxostat: the manufacturer advises against concomitant use

Baclofen

Baclofen was first marketed in the UK in the early 1970s, following promising trial results in patients with spasticity secondary to MS. Along with tizanidine, it remains a first-line treatment for spasticity of both cerebral and spinal origin. Oral baclofen has low CSF penetrance, and thus side effects can be problematic for many patients at the doses required for therapeutic response. In 1984, Penn and Kroin reported in *The Lancet* that administration of low-dose baclofen directly into the subarachnoid space reduced spasticity, with significantly reduced side effects. Continuous intrathecal infusion of baclofen (ITB) has since become a widely adopted treatment for both chronic spasticity and dystonia.

Uses

1. Oral baclofen.

Licensed uses

In the UK

- *Spasticity*: baclofen is licensed for the treatment of voluntary muscle spasticity secondary to cerebral disorders (such as meningitis, stroke, and traumatic head injury) and spinal disorders (including MS and MND) in individuals of all ages.

In the USA

- *Spasticity*: baclofen is licensed for the treatment of spasticity associated with spinal cord diseases and injuries, including MS (but not stroke, cerebral palsy, or PD), in individuals of all ages.

Off-licence uses

- Bladder spasticity and dystonia (particularly useful in segmental forms and childhood dystonic gait).

2. Intrathecal baclofen.

Licensed uses

In the UK/USA

- *Spasticity*: for use by specialist units to treat severe, chronic spasticity of cerebral or spinal origin unresponsive to oral therapy or if side effects of oral therapy not tolerated in individuals over the age of 4.

In the UK, patient selection criteria are clearly defined by commissioning boards.

Off-licence uses

- Severe generalized dystonia (particularly if concomitant severe spasticity).

Presentation

- *Trade names*:
  1. oral: Gablofen®, Lioresal®, and Lyflex®. Generics are available;
  2. intrathecal: Lioresal®. Generics are not available.
- *Formulations*: baclofen is available as an oral solution and tablet. Oral solution: 5mg/5mL oral solution in 300mL units. Tablet: 10mg and

20mg. Intrathecal baclofen is available as a solution for injection in 1mL ampoules of 50 micrograms/mL (for test doses), and 5mL (2mg/mL) and 20mL (500 micrograms/mL) ampoules (for use with implantable pumps).

Mechanism of action

Baclofen exhibits affinity for both pre- and post-synaptic $GABA_B$ receptors and acts predominantly at the spinal cord level. Activation of presynaptic $GABA_B$ receptors leads to axonal hyperpolarization. This reduces the chance of depolarization and subsequent exocytosis of excitatory neurotransmitters into the synaptic cleft. Stimulation of post-synaptic $GABA_B$ receptors similarly leads to cell hyperpolarization, thus preventing action potential propagation.

Intrathecal delivery is via an adjustable, implantable pump (typically situated subcutaneously or subfascially in the lateral abdominal wall) with a tunnelled spinal catheter. The most commonly used pump devices are the battery-powered SynchroMed® series (typical battery lifespan is 7 years). This method of delivery allows maximal concentration of baclofen to be achieved at the target spinal $GABA_B$ receptors, while minimizing systemic side effects.

Toxicity and side effects

- *Common—cardiovascular*: decreased cardiac output, hypotension. *Dermatological*: hyperhidrosis, rash, urticaria. *Endocrine*: hyperglycaemia. *Gastrointestinal*: constipation, diarrhoea, LFT derangement, nausea, retching. *Musculoskeletal*: myalgia. *Neurological*: ataxia, confusion, dizziness, headache, muscle weakness, nystagmus, sedation. *Ophthalmological*: accommodation disorders, visual impairment. *Psychiatric*: depression, euphoria, hallucinations, insomnia, nightmares. *Urological*: dysuria, enuresis.
- *Serious*: serious adverse effects are thought to be commoner with spasticity secondary to stroke. *Neurological*: paradoxical increased spasticity and seizures. *Respiratory*: respiratory depression.

Intrathecal

- *Test dosing*: nausea, vomiting, dizziness, headache, transient hypotonia, sedation, and urinary retention are common. Rarely, even small doses can induce coma; hence resuscitation facilities are required.
- *Pump implantation*: common post-operative side effects include headache, constipation, and CSF leakage or collection. The risk of bacterial meningitis is ~1%. The long-term risk of localized pump infection is ~10% (subfascial pumps may be less prone to infection than SC ones). There are several case reports of catheter tip granulomas which can cause neurological impairment.
- *Overinfusion*: typically occurs following errors with pump refilling or reprogramming, causing overdose. Clinical signs develop rapidly and include sedation, hypotonia, hypotension, bradycardia, and respiratory depression. Convulsions, rhabdomyolysis, and prolonged coma can result. Treatment is supportive, in an intensive care environment,

while the pump is immediately stopped and drained. Therapeutic CSF drainage is often performed, although its efficacy is uncertain.

- *Underinfusion*: typically occurs due to catheter blockage/disconnection (common—especially in the first year) or depletion of baclofen, rarely due to pump malfunction. This can lead to the potentially fatal baclofen withdrawal syndrome within hours or days (clinically resembling NMS)—hyperthermia, muscle spasm, rigidity and later convulsions, status epilepticus, rhabdomyolysis, coagulopathy, and multiple organ failure. Early symptoms include pruritus, paraesthesiae, and hypotension. Treatment is supportive. Intrathecal infusion should be restored as soon as possible—PO baclofen and IV benzodiazepines can be used as a temporary measure. Electromagnetic interference can also cause a transient pump stall, potentially leading to underinfusion—this is known to occur during MRI. While this does not exclude ITB patients from undergoing MRI, patients should have their pump status checked immediately after scanning.
- *Drug-related side effects*: systemic effects are not totally eliminated with intrathecal therapy.

Contraindications

- *Absolute*: hypersensitivity to baclofen, active peptic ulceration, porphyria.
- *Relative*: use with caution in patients with severe psychiatric disorders (possible exacerbation), concomitant antihypertensive therapy (risk of profound hypotension), epilepsy (may lower seizure threshold), history of peptic ulceration (stimulates gastric acid secretion), end-stage renal failure (risk of overdose), and urinary sphincter hypertonia (risk of acute retention). Baclofen is predominantly renally excreted; use smaller doses, e.g. 5mg/day, in renal impairment. If eGFR is <15mL/min/1.73m^2, use with caution, only if potential benefits exceed risks. In hepatic impairment, use with caution, but no dose adjustment is routinely recommended.

Uses in special populations

- *Elderly*: older patients may be more prone to sedation and hypotension; thus, close monitoring and careful dose titration are advised.
- *Pregnancy*: baclofen crosses the placental barrier. While there have been no reports of teratogenic effects in humans, use in the first trimester should be avoided. Use with caution in later pregnancy, as use may be associated with withdrawal symptoms in the infant.
- *Lactation*: baclofen is secreted in breast milk in minute quantities. No adverse events have been reported.

Efficacy

1. Oral.

Numerous low-quality trials have investigated the use of baclofen in the treatment of dystonia and spasticity. True meta-analysis of these trials has proven difficult, due to their heterogeneity, with regard to both the test subjects' underlying conditions and the outcome measures used. There

is therefore a lack of robust comparative evidence to support the use of baclofen over other agents.

- *Dystonia*: baclofen has been found to be effective in the treatment of dystonia in retrospective studies and case reports, with a greater effect in children than adults. One series ($n = 358$) assessed the effectiveness of baclofen on patients following initial treatment with an anticholinergic. Here, 20% of patients with various forms of dystonia had a good response to oral baclofen. Factors associated with a good response were those with mild to moderate dystonia and age <20.
- *Spasticity*: a 2004 systematic review investigated whether baclofen was superior to placebo. Out of 14 trials from 1977 to 2000, ten found in favour of oral baclofen vs placebo for spasticity of various aetiologies (but predominantly MS). Outcome measures included improvements in Ashworth scores in some trials, but most used non-validated outcomes. A 2003 review of anti-spasticity agents used in MS found no difference in efficacy between baclofen and diazepam. A 1998 meta-analysis of ten previously unpublished trials found baclofen to be of comparable efficacy to tizanidine and diazepam (participants were predominantly MS patients).

2. Intrathecal.

A number of case series have shown impressive improvements in Ashworth scores in patients previously unresponsive to oral therapy. Placebo-controlled trials are lacking, due to the nature of the delivery system; however, one Dutch centre has conducted a small RCT (the two study arms commenced ITB 6 months apart) finding in favour of ITB vs continuing oral therapy. Many centres have published positive long-term follow-up data over the last two decades, and this is increasingly being supported by favourable meta-analyses of functional outcomes. The cost/benefit ratio has been explored extensively and appears favourable for patients with good carer support who exhibit poor response to oral therapy.

Dosing and monitoring

Dosing

1. Oral.
   - *Dystonia*: start treatment at 5mg at night, and increase the dose by 5mg every week to reach 10mg tds. The usual maintenance dose ranges from 60 to 100mg/day.
   - *Spasticity*: start treatment at 5mg tds. This can be increased by 5mg tds at 3-day intervals.

Symptoms are usually controlled at doses of 20mg tds or less. Maximum total daily dose should not exceed 100mg. Discontinuation is advised if no response occurs after 6 weeks of therapy.

Administration with meals may reduce gastrointestinal side effects. Regular review of therapeutic response and sedative side effects is required during the initial titration period.

Discontinuation Abrupt cessation of baclofen can lead to rebound spasticity, as well as physiological and psychiatric symptoms of withdrawal, particularly following long-term therapy. Therefore, a gradual downward tapering of dosage over a period of at least 7–14 days is advised.

2. Intrathecal.

(Below are the manufacturer's guidelines. Some centres may have their own protocols.)

Test dosing All patients require test dosing before consideration for long-term ITB. An initial 25-microgram dose is administered via an LP over a minimum of 1min in a fully monitored environment. Further test doses can be administered at 24h intervals, increasing in 25-microgram increments up to a maximum of 100 micrograms. Patients should be observed continuously for a reduction in spasticity lasting 4–8h.

Dosing Following pump implantation, the initial daily dose is as follows:

- *patients with a response to test dose lasting <12h*: double the initial test dose infused continuously over a 24h period;
- *patients with a response to test dose lasting >12h*: the initial test dose infused continuously over a 24h period.

Titration Daily infusion doses should be increased by 10–20% no more quickly than every 24–48h, until a satisfactory response has been achieved. Patients with spasticity of cerebral origin may require more cautious uptitration. Maintenance doses of 300 micrograms/24h are typical in patients with cerebral spasticity. Patients with spinal spasticity often require higher doses of up to 800 micrograms/24h. Doses of up to 2mg/24h have been used.

Patients should be well established on a suitable daily infusion dose, before more complex regimes, such as overnight boosting, are attempted.

Discontinuation Discontinuation should proceed by gradual downward titration of the daily infused dose to prevent baclofen withdrawal syndrome.

Routine monitoring Patients require regular follow-up for reservoir refilling and often need a gradual increase in the daily infusion dose over time. Again, this should proceed in 10–20% increments.

Pharmacokinetics and interactions

Pharmacokinetics

The oral preparation has a bioavailability of ~100%. Peak plasma concentrations occur at 2–3h. Ingestion with food does not affect bioavailability. Approximately one-third of the absorbed medication is bound to serum proteins. Baclofen penetrates the blood–brain barrier to reach the CSF where concentrations are 10–12% of the serum level. The half-life is 3–4h in the serum, and 5h in the CSF. ~15% of an oral dose undergoes deamination in the liver to form a pharmacologically inactive metabolite. The remaining 85% is excreted unchanged in urine.

With regard to intrathecal pharmacokinetics, there is significant inter-patient variability. At typical intrathecal infusion rates, steady-state CSF concentrations are reached within 1–2 days and vary between 100 and 1000ng/mL. Plasma concentrations are typically <5ng/mL. Bolus-dose half-life is in the region of 1–4h. CSF clearance is ~30mL/h.

Interactions See Table A.53.

Table A.53 Interactions of baclofen

Pharmacodynamic interactions
With antihypertensives: increased risk of hypotension
With CNS depressants, e.g. alcohol: potential for increased sedative effects
With dopaminergics and lithium: avoid levodopa, as confusion, hallucinations, and headaches can be profound; lithium can aggravate hyperkinetic symptoms
With TCAs: can cause muscle hypotonia and increased sedative side effects

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Betahistine

Betahistine hydrochloride was first used in the treatment of Ménière's disease in the 1960s. It is a histamine analogue which acts as a H1 receptor agonist and a H3 receptor antagonist. It remains widely used in Europe for the management of vertigo and other symptoms associated with Ménière's disease.

Uses

Licensed uses

In the UK

- *Vertigo*: betahistine is licensed for the treatment of Ménière's disease in individuals aged 18 years and older.

Betahistine is not licensed for use in the USA.

Off-licence uses

- Vertigo of vestibular origin.

Presentation

- *Trade names*: Serc®. Generics are available.
- *Formulations*: betahistine is available as a tablet in 8mg, 16mg, and 24mg doses.

Mechanism of action

Betahistine is a weak H1 receptor agonist and a strong H3 receptor antagonist. Agonistic effects at H1 receptors on the pre-capillary sphincter in the stria vascularis of the inner ear result in vasodilatation and increased vascular permeability, thereby reducing the associated pressure of endolymphatic hydrops seen in Ménière's disease. H3 receptors are inhibitory autoreceptors; thus, the antagonism of betahistine at this site is believed to stimulate histamine release, thereby increasing the action of histamine at H1 receptors and reducing hydrostatic pressure within the inner ear.

Toxicity and side effects

- *Common—gastrointestinal*: dyspepsia and nausea.
  Neurological: drowsiness and headache.
- *Serious—cardiovascular*: palpitations. *Dermatological*: anaphylaxis, angio-oedema, and Stevens–Johnson syndrome have been reported. *Gastrointestinal*: peptic ulcer disease.

Contraindications

- *Absolute*: hypersensitivity to betahistine or its excipients and phaeochromocytoma.
- *Relative*: bronchial asthma, peptic ulcer disease, severe hypotension, and patients with pre-existing urticaria, rashes, or allergic rhinitis, as all of these conditions may be exacerbated by betahistine. No dosage adjustment is routinely recommended for patients with hepatic or renal impairment in the product literature—use with caution.

Uses in special populations

- *Elderly*: no dose adjustment is required. Use with caution, as the elderly are more prone to side effects and have an age-related impairment in hepatic and renal function.
- *Pregnancy*: animal reproductive studies have shown no adverse effects; however, as a precaution, manufacturers advise avoiding use during pregnancy.
- *Lactation*: it is not known if betahistine is excreted in breast milk. As a precaution, the manufacturers advise avoiding use in nursing mothers.

Efficacy

Betahistine is commonly used for the treatment of Ménière's disease in the UK; however, supporting evidence for its use is of poor quality, and, for this reason, betahistine is not licensed in the USA. A 2011 Cochrane review of seven trials (243 patients with Ménière's disease) found that there was insufficient evidence of any beneficial effect of betahistine on symptoms. Although most trials suggested a reduction in vertigo (and, to a lesser, extent tinnitus), the Cochrane review concluded these effects may have arisen due to bias in the methodology of the trials.

Dosing and monitoring

Dosing

Initial dose is 8–16mg tds with food. The usual maintenance dose is 24–48mg/day.

Routine monitoring None is required.

Pharmacokinetics and interactions

Pharmacokinetics

The oral bioavailability of betahistine is ~100%. T_{max} is 1h; this is delayed with food co-ingestion. Binding with plasma proteins is <5%. It is metabolized to 2-pyridylacetic acid, an inactive metabolite, by the liver. Ninety-one per cent is excreted in the urine as inactive metabolites. The elimination half-life of 2-pyridylacetic acid is ~3.5h.

Interactions See Table A.54.

Table A.54 Interactions of betahistine

Medications which alter betahistine plasma levels	Pharmacodynamic interactions
Levels increased: MAOIs	With antihistamines: theoretically, the effects of betahistine are antagonized by antihistamines

Reference

James A, Burton MJ. Betahistine for Ménière's disease or syndrome. *Cochrane Database Syst Rev* 2001;1:CD001873.

β-interferon

IFN-β1b was the first drug demonstrated to reduce relapse rates in RRMS. The pivotal trial was published in 1993, and IFN-β remains a first-line therapy in RRMS. Its advantages are an established history of use and experience in MS over the last 20 years, however it requires regular injections and is relatively commonly associated with flu-like side effects, making newer oral disease modifying agents a more attractive alternative for many.

Uses

Licensed uses

In the UK/USA

- *RRMS*: Avonex®, Betaferon®/Betaseron®, Extavia®, Plegridy® and Rebif® are licensed for patients with RRMS. In the UK, this requires two or more relapses in the previous 2 years (or 3 years for Avonex®), without evidence of disease progression between relapses.
- *Clinically isolated syndrome*: these drugs are also licensed for patients with a single demyelinating event with an active inflammatory process. In the USA, MRI features consistent with MS are required, and Rebif® is not licensed for such cases. In the UK, diagnoses other than MS must be excluded, the event must be severe enough to warrant treatment with IV corticosteroids, and the patient should be deemed to be at high risk of developing clinically definite MS. Rebif® therapy is licensed for this use in the UK.

Presentation

- *Trade names*: Avonex®, Betaferon®/Betaseron®, Extavia®, Plegridy®, and Rebif®. Generics are not available.
- *Formulations*: IFN-β1a is available as a solution for injection in cartridges, pre-filled syringes, or vials. Cartridges (Rebif®): 22 and 44 micrograms. Pre-filled syringes and vials (Avonex®): 30mg, (Plegridy®): 63, 94, and 125 micrograms. IFN-β1b is available as vials of powder with solvent. Vials (Betaferon®/Betaseron® and Extavia®): 300mg.

Mechanism of action

IFN-β is a cytokine produced by macrophages and fibroblasts. Exogenous IFN-β can be further subdivided into IFN-β1a or 1b. These differ structurally through subtle variations in amino acid sequence and glycosylation state. They bind to type I IFN receptors and induce a multitude of transcriptional changes. These result in reduced expression of various pro-inflammatory cytokines and upregulation of the expression of anti-inflammatory cytokines. Plegridy® is a pegylated version of interferon beta-1a, whose pegylated structure results in a slower rate of metabolism and hence once fortnightly dosing, compared to a higher rate of administration with alternative interferon based drugs.

Toxicity and side effects

- *Common—dermatological*: increased sweating, injection site pain/erythema, flushing, and a rash. *Endocrine*: elevated serum potassium. *Gastrointestinal*: anorexia, diarrhoea, deranged LFTs, nausea, and vomiting. *Haematological*: decreased lymphocyte and neutrophil counts.

Immunological: fever, flu-like symptoms, malaise, and night sweats. *Musculoskeletal*: arthralgia, back pain, muscle cramping/stiffness, and myalgia. *Neurological*: headache, hypoesthesia, and muscle spasticity. *Psychiatric*: depression and insomnia. *Respiratory*: rhinorrhoea.

- *Serious—cardiovascular*: congestive cardiac failure. *Dermatological*: injection site infection/necrosis. *Gastrointestinal*: hepatitis and pancreatitis. *Haematological*: capillary leak syndrome if pre-existing monoclonal gammopathy and TTP or HUS have been reported. *Immunological*: anaphylaxis.

Contraindications

- *Absolute*: treatment initiation during pregnancy, hypersensitivity, severe depression, suicidal ideation, and specifically for IFN-β1b (Betaferon®/Betaseron® and Extavia®) decompensated liver disease.
- *Relative*: caution should be used in patients with any hepatic impairment and severe renal impairment, in whom close monitoring is advised.

Uses in special populations

- *Elderly*: IFN-β has not been extensively studied in the elderly. However, this group has an age-related deterioration in hepatic and renal function; hence caution is required.
- *Pregnancy*: it is advised that women can continue treatment during attempted conception, but IFN-β should be stopped when pregnancy is confirmed. Treatment initiation is contraindicated in pregnancy.
- *Lactation*: IFN-β should not be used, while breastfeeding.

Efficacy

An approximate decrease in the ARR of 30% was shown for IFN-β1b (Betaferon®/Betaseron®), IM IFN-β1a (Avonex®), and SC IFN-β1a (Rebif®) in the pivotal trials (IFN-MS Study Group, MSCRG, and PRISMS). Several comparison trials have suggested slight superiority of high-dose, frequently administered SC IFN-β, compared to lower-dose, weekly IM IFN-β (INCOMIN and EVIDENCE trials). However, development of neutralizing antibodies appears lower with IM IFN-β, possibly negating this effect. Broadly, the efficacy of all injectable agents is considered comparable.

Dosing and monitoring

Dosing

Avonex® is a once-weekly IM dose of 30 micrograms. Rebif® is a three times per week SC dose of 22 or 44 micrograms. Betaferon®/Betaseron® and Extavia® are given SC on alternate days at a dose of 250 micrograms. This dosing should be titrated up as 62.5 micrograms for the first three doses, 125 micrograms for the second three doses, 187.5 micrograms for the next three doses, and then 250 micrograms from then onwards. Plegridy® is administered by a prefilled pen for SC injection. The first dose is 63 micrograms, the second at day 14 is 94 micrograms and the third at day 28 is 125 micrograms. Fortnightly 125 microgram injections are the usual maintenance dose.

Routine monitoring

FBC and LFT monitoring is required before and during therapy at 1 and 3 months, and then 6-monthly. Elevation of liver enzymes of five times

the upper limit of normal or with clinical symptoms of hepatic impairment should prompt dose reductions or treatment cessation. TFT and immunoglobulin levels should be checked prior to initiation. Practices of monitoring neutralizing antibodies against IFN-β vary. Some specialists advocate routine measurement, and others only when clinical response to treatment is suboptimal. No data exist to support the need for a washout period before starting alternative immunomodulatory therapy. It is generally stopped for 4–6 weeks before initiating natalizumab treatment, but no washout period is necessary if switching to glatiramer acetate or fingolimod.

Pharmacokinetics and interactions

Pharmacokinetics

IM IFN-β1a demonstrates peak activity between 5h and 15h and has a bioavailability that varies with injection site of ~40%. SC IFN-β1a has a peak serum concentration at 3h, and SC IFN-β1b has a peak serum concentration at 1–8h. The absolute bioavailability of SC IFN-β1b is ~50%. After multiple doses of SC IFN-β1b, there are no increases in serum concentration. The metabolism of IFN-β is poorly described; it is metabolized and excreted by both the liver and the kidneys. The half-life is highly variable between preparations and can be between 10h and 70h. Pegylated interferon (Plegridy®) reaches T_{max} at 1–1.5 days post dose and has a half-life of 78 +/– 15 hours, ~2x longer than non-pegylated interferon beta-1a.

Interactions None.

References

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Bevacizumab

Bevacizumab is an anti-angiogenic medication, first successfully trialled in humans in 1997. In the context of neuro-oncology, its use is predominantly in the treatment of metastatic solid organ tumours, although the Food and Drug Administration (FDA) have recently extended its labelling to treatment-refractory glioblastoma.

Uses

Licensed uses

In the UK/USA

- *Metastatic disease*: bevacizumab is licensed as part of a multi-agent chemotherapy regime in the treatment of the following metastatic malignancies, including colorectal, non-squamous non-small cell lung, and renal cancer, in individuals aged 18 years and older.

In the USA

- *Glioblastoma*: bevacizumab is licensed as a second-line, single-agent therapy in individuals aged 18 years and older with progressive disease.

Off-licence uses

- Meningioma and radiation necrosis.

Presentation

- *Trade names*: Avastin®. Generics are not available.
- *Formulations*: bevacizumab is available as a concentrate for IV infusion at 25mg/mL in 100 and 400mg vials.

Mechanism of action

Bevacizumab is a humanized monoclonal antibody, which selectively binds all isoforms of VEGF, preventing binding to its receptors VEGFR-1 and 2. The VEGF pathway mediates angiogenesis and vascular permeability. As a highly vascularized tumour, glioblastoma requires high levels of angiogenesis to maintain rapid growth. Blockade of this pathway is thought to inhibit tumour growth and reduce vascular permeability, thereby minimizing peritumoural vasogenic oedema. A lack of specificity for neoplastic tissues is responsible for much of its adverse event profile.

Toxicity and side effects

- *Common—cardiovascular*: hypertension is very common and dose-dependent. Congestive heart failure and supraventricular tachycardia are common. *Dermatological*: dry skin, delayed wound healing, exfoliative dermatitis, palmar–plantar erythrodysaesthesia syndrome, and skin discoloration. *ENT*: epistaxis and rhinitis. *Gastrointestinal*: anorexia, change in bowel habit, nausea, stomatitis, and vomiting. *Haematological*: anaemia, leucopenia, and thrombocytopenia. *Musculoskeletal*: arthralgia, muscular weakness, and myalgia. *Neurological*: dysarthria, headache, fatigue, peripheral sensory disturbance, and syncope. *Ophthalmological*: eye disorders. *Renal*: proteinuria, usually not associated with renal dysfunction,

although nephrotic syndrome was identified in up to 1.4% of patients, and UTIs. *Respiratory*: dyspnoea.

- *Serious—cardiovascular*: arterial thromboembolism, deep vein thrombosis, and haemorrhage. *Dermatological*: necrotizing fasciitis can develop in poorly healing wounds. *Endocrine*: risk of ovarian failure in premenopausal women is ~40%. Reversible after treatment discontinuation in the majority (86%). *Gastrointestinal*: abdominal perforation can occur. The highest incidence is in patients treated for colorectal cancer where the likelihood of abscess, fistula development, or perforation was up to 2.7%. Ileus and intestinal obstruction are other potentially serious side effects. *Immunological*: anaphylactic reactions. *Musculoskeletal*: osteonecrosis of the jaw. *Neurological*: cerebrovascular accident and posterior reversible encephalopathy syndrome.

Contraindications

- *Absolute*: hypersensitivity to any active constituent of the medication, and pregnancy.
- *Relative*: caution in patients with intra-abdominal inflammatory conditions, fistulae, poorly controlled congestive heart failure, or hypertension, and patients with previous history of arterial or venous thromboembolism. Due to poor wound healing and the potential risk of necrotizing fasciitis, bevacizumab should be stopped, ideally for at least 28 days, prior to elective surgery. Bevacizumab should be used with caution in patients with poor dental health or using bisphosphonates, due to the potential risk of osteonecrosis of the jaw.

No specific caution is required in renal or hepatic impairment.

Uses in special populations

- *Elderly*: elderly patients are at higher risk of developing arterial thromboembolic complications and blood dyscrasias, compared to younger patients. They are also more likely to have underlying hypertension and congestive heart failure requiring careful monitoring during treatment.
- *Pregnancy*: animal studies have demonstrated teratogenicity; hence bevacizumab is contraindicated in pregnancy. It should be avoided for at least 6 months prior to conception.
- *Lactation*: no studies have assessed whether bevacizumab is present in human milk; however, human IgG is known to be present. It is advised to avoid breastfeeding for at least 6 months following administration of bevacizumab.

Efficacy

Bevacizumab has demonstrated efficacy in two single-arm, open-label studies investigating previously treated glioblastoma. In both studies, treatment was second-line, following prior treatment with temozolomide and radiotherapy. Objective response, based on MRI criteria, was found in 20–26% of patients.

Dosing and monitoring

Dosing

The dosage of bevacizumab varies, depending on body weight, clinical indication, local protocols, and adjuvants used in the chemotherapy regimen. Readers are advised to follow local guidelines. Doses can vary from 7.5mg/kg to 15mg/kg and are usually given at 2- to 3-weekly intervals. The number of cycles depends on the specific chemotherapy regimen.

Routine monitoring

Prior to initiation of treatment, BP, FBC, and urinary protein should be assessed. These should be monitored throughout treatment, as per local chemotherapy guidelines.

Pharmacokinetics and interactions

Pharmacokinetics

The pharmacokinetics of bevacizumab are linear at doses of 1–10mg/kg. Metabolism is similar to that of an endogenous IgG molecule, i.e. endothelial cell-mediated proteolysis throughout the body. The half-life is, on average, 18 days for a female patient and 20 days for a male patient. Clearance is accelerated by elevated tumour burden (7%) and low albumin levels (30%).

Interactions See Table A.55.

Table A.55 Interactions of bevacizumab

Pharmacodynamic interactions
With cytotoxics: increased rates/severity of blood dyscrasias
With sunitinib malate: microangiopathic haemolytic anaemia can occur

References

Cloughesy T, Vredenburgh J, Day B, *et al*. Updated safety and survival of patients with relapsed glioblastoma treated with bevacizumab in the BRAIN study. *J Clin Oncol* 2010;**28**(15):1.

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Botulinum toxin A (and B)

Clostridium botulinum bacteria produce seven toxins, of which A and B are available commercially for their muscle-relaxing properties. Botulinum toxin type A was the first toxin identified and was initially used in the treatment of strabismus, as far back as the 1980s. Today, it is used for a wide range of medical conditions, as well as forming the basis of a multi-billion dollar cosmetic industry.

Uses

Licensed uses

In the UK

- *Blepharospasm, hemifacial spasm, and idiopathic cervical dystonia*: BTX-A is licensed for the treatment of these conditions in individuals aged 12 years and older.
- *Migraine*: BTX-A is licensed for the prophylaxis of chronic migraine in individuals aged 18 years and older.
- *Spasticity*: BTX-A is also licensed for the treatment of focal spasticity in ambulant cerebral palsy individuals aged 2 years and older, and post-stroke spasticity in individuals aged 18 years and older.

In the USA

- *Blepharospasm and strabismus*: BTX-A is licensed for the treatment of these conditions in individuals aged 12 years and older.
- *Migraine*: BTX-A is licensed for the prophylaxis of chronic migraine in individuals aged 18 years and older.
- *Spasticity*: BTX-A is licensed for the treatment of upper limb spasticity in individuals aged 18 years and older.

Off-licence uses

- ET, dystonia, and spasticity affecting other body parts, neuropathic pain, tension headaches, and tic disorders.

Presentation

The pharmaceutical preparation comprises the active polypeptide associated with a number of accessory proteins which differ between manufacturers. Each manufacturer utilizes different quantification systems, all qualified as 'units'. These are preparation-specific and must not be interchanged between brands.

- *Trade names*:
  - medical brands: Botox®, Dysport®, and Xeomin®;
  - cosmetic brands: Azzalure®, Bocouture®, Botox Cosmetic®, and Vistabel®. Generics are not available.
- *Formulations*: BTX-A is available as a powder for reconstitution with sodium chloride solution and subsequent injection in 100 and 500 unit vials.

Mechanism of action

BTX-A blocks the release of acetylcholine at the presynaptic NMJ, causing a chemical denervation leading to muscle relaxation. It degrades the synaptosome-associated protein-25 (SNAP-25) protein, which is required for vesicle formation and neurotransmitter release. The mechanism by which BTX-A produces analgesia is under debate. It has been postulated that it induces its analgesic effect independent of its action on muscle tone, possibly involving blocking mediators of neurogenic inflammation (e.g. substance P, glutamate, calcitonin gene-related peptide), and thus peripheral and central sensitization to painful stimuli.

Botulinum toxin type B

BTX-B has a similar effect, but a different target, when compared to type A, i.e. it cleaves the synaptic vesicle-associated membrane protein (VAMP, also known as synaptobrevin), which is a component of the protein complex responsible for docking and fusion of the synaptic vesicle to the presynaptic membrane, preventing neurotransmitter release, whereas type A toxin cleaves SNAP-25 (see Mechanism of action above) and has similar effects on neurotransmitter release. Type B was discovered after type A and hence has a smaller evidence base. It is licensed only for the treatment of cervical dystonia (in both the UK and USA) where significant improvements similar to that with the type A toxin have been found. No large comparative studies have been published so far looking at differences in the two toxins, although it is thought that type B toxin may have a shorter duration of effect. In light of this and the markedly stronger evidence base for type A toxin, type B toxin is generally used second-line in patients with resistance/neutralizing antibodies developing during treatment with type A toxin.

Toxicity and side effects

On administration of botulinum toxin, there may be increased electrophysiologic jitter in some distant muscles; misplaced injections may paralyse nearby muscle groups, and excessive doses may paralyse distant muscles. Influenza-like symptoms are common. Local injection site side effects will vary, dependent on the area of the body treated.

- *Common—dermatological*: dermatitis, ecchymosis, facial oedema. *Gastrointestinal*: dry mouth. *Neurological*: facial droop, headache. *Ophthalmological*: dry eye, ectropion, entropion, keratitis, ptosis.
- *Serious—cardiovascular*: arrhythmias, MI. *Dermatological*: anaphylaxis. *Ophthalmological*: angle-closure glaucoma, corneal ulceration/perforation. *Neurological*: aspiration, dysphagia, and seizures.

Contraindications

- *Absolute*: generalized disorders of muscle activity, e.g. MG, infections at injection site.
- *Relative*: history of dysphagia or aspiration.

No dose adjustment is necessary in hepatic or renal failure.

Uses in special populations

- *Elderly*: no dose adjustment required.
- *Pregnancy*: there have been no reported side effects when used in pregnancy, although there are limited studies. Low risk of systemic absorption. Use if the benefits outweigh the risks to the fetus.
- *Lactation*: low risk of systemic absorption. No studies performed, although one report of an infant successfully breastfed, with no consequences. Generally recognized as safe, as long as the infant does not come into contact with the area of skin injected with BTX-A. Do not inject the skin around the breast.

Efficacy

- *Dystonia*: BTX-A has undergone several open-label trials and RCTs to assess its efficacy in the treatment of focal dystonia. It has been shown to be effective in up to 90% of patients with blepharospasm and, for this reason, is considered first-line. Several RCTs have compared the efficacy of different formulations of BTX-A, with no clear difference noted between the agents. RCTs showing significant improvement in symptoms have also been conducted for cervical, limb, laryngeal, and oromandibular dystonia.
- *Migraine*: in one RCT ($n = 123$), patients receiving botulinum toxin reported significantly fewer migraine attacks and reduced severity of headache vs placebo. Botulinum toxin has not been shown to be effective in episodic migraine.
- *Neuropathic pain*: there have been a number of small placebo-controlled trials that demonstrated BTX-A injection could produce significant pain relief in patients with peripheral nerve injury, painful diabetic neuropathy, post-herpetic neuralgia, and post-traumatic neuropathic pain. Analgesic effect usually lasts 3 months. Larger RCTs and meta-analyses are awaited to substantiate these findings.
- *Spasticity*: a 2008 meta-analysis of 13 randomized, placebo-controlled trials totalling 891 subjects concluded that BTX-A was safe and effective in treating focal spasticity of both upper and lower limbs in adults (grade I evidence). Outcome measures included improvements in Ashworth scores, range of motion, cleaning, hygiene, and pain. Use in upper limb spasticity is supported by a recent Cochrane Centre review.

Dosing and monitoring

Dosing

The product literature of the chosen preparation should be consulted for detailed guidance regarding dosing and administration, depending upon the specific indication.

In neuropathic pain, there is currently no recommended dosing strategy by professional bodies. A recent descriptive review analysed dosing strategies in all trials performed up to 2013. Please see this for further information with regard to dosing strategies in the treatment of neuropathic pain.

Routine monitoring

Successful treatment should cause therapeutic benefit within days and last for 3–4 months on average.

In the context of spasticity, electrophysiological investigation may be warranted if no clinical improvement is seen after 1 week, and multidisciplinary assessment of functional capacity and therapeutic effect should take place after each course of treatment.

It is estimated that 3–10% of patients may be resistant to the beneficial effects of BTX-A therapy due to antibody formation against the toxin and/or the associated accessory proteins. This is more likely to occur following frequent administration of high doses. Serum antibody assays are available, should this be suspected. Electrophysiological studies may help to exclude resistance, while other botulinum toxin serotypes may be of use as second-line therapy (BTX-B is currently the only other commercially available serotype).

Pharmacokinetics and interactions

Pharmacokinetics

Not present in peripheral blood at measurable levels following IM or intradermal injection. Light chains of BTX-A are cleaved by SNAP-25. The half-life of BTX-A is ~31 days, based on *in vitro* studies. Clinical effect wears off within 3 months. Antibody formation leads to deterioration in response.

Interactions See Table A.56.

Table A.56 Interactions of BTX-A (and B)

Pharmacodynamic interactions
With aminoglycoside antibiotics: may potentiate the effect of botulinum toxin
With anticoagulants and antiplatelet drugs: increased risk of bleeding at the injection site
With anticholinergic drugs: increased anticholinergic side effects
With muscle relaxants: increased risk of muscular weakness

References

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Candesartan

Candesartan is an angiotensin receptor blocker (ARB), commonly used in hypertension and heart failure. Candesartan and other medications which act on the renin–angiotensin–aldosterone system, such as ACE inhibitors and other ARBs, have been shown to be of some benefit in the prophylaxis of migraine.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- Candesartan is used in the management of heart failure and hypertension. There is no licensed neurological use.

Off-licence uses

- Migraine prophylaxis in adults.

Presentation

- *Trade names*: Amias®, Atacand®. Generics are available.
- *Formulations*: candesartan is available as a standard tablet. Standard tablets: 2mg, 4mg, 8mg, 16mg, and 32mg.

Mechanism of action

Angiotensin II receptors are present on neurons, cerebral endothelial cells, and astrocytes. These receptors alter cerebral blood flow by a number of mechanisms: modulation of potassium and calcium receptor activity, increases in cerebral levels of dopamine and 5-hydroxyindoleacetic acid (5-HIAA), a serotonin metabolite, and increases in the production of inducible NO synthase. All of these actions of angiotensin II receptors may be involved in the pathogenesis of migraine.

Toxicity and side effects

- *Common—neurological*: dizziness, headache, vertigo. *Renal*: impaired renal function and hyperkalaemia. *Respiratory*: cough.
- *Serious—gastrointestinal*: deranged LFTs, hepatitis. *Haematological*: agranulocytosis, leucopenia, neutropenia. *Immunological*: angio-oedema.

Contraindications

- *Absolute*: hypersensitivity to candesartan. Candesartan should not be co-administered with aliskiren, a direct renin inhibitor, in patients with diabetes. Avoid in severe hepatic impairment.
- *Relative*: aortic/mitral valve stenosis, hypertrophic cardiomyopathy, and renal artery stenosis. In mild/moderate hepatic impairment and renal impairment, the starting dose is 4mg. Increase cautiously, with regular monitoring of renal function.

Uses in special populations

- *Elderly*: elderly patients may require a smaller starting dose, with slower drug uptitration.

- *Pregnancy*: candesartan is contraindicated in pregnancy. In the second and third trimester, it has been shown to impair fetal renal function, leading to oligohydramnios, lung hypoplasia, skeletal abnormalities, and intrauterine death.
- *Lactation*: there are limited data on the safety of candesartan in breastfeeding. It should be avoided in breastfeeding mothers.

Efficacy

Candesartan was compared to placebo in a randomized, double-blind cross-over trial of 60 patients. Patients received 16mg of candesartan or placebo for 12 weeks and then crossed over to the other arm for another 12 weeks. The primary endpoint was the number of days with headache. Candesartan was significantly more effective than placebo, with fewer headache days (13.6 vs. 18.5, respectively; $p = 0.001$) and total hours with headache (95 vs 139, respectively; $p < 0.001$).

Dosing and monitoring

Dosing

The dose of candesartan in migraine prophylaxis is 16mg od. Patients can be started on 8mg od, which can be increased, as tolerated, to 16mg.

Routine monitoring

BP and renal function should be assessed before starting therapy and regularly during treatment.

Pharmacokinetics and interactions

Pharmacokinetics

Candesartan is a prodrug and is hydrolyzed to its active form on absorption. It is 99% bound to plasma protein and reaches peak plasma concentration at 3–4h. The bioavailability of the tablet form is 14%. The majority of the drug is excreted unchanged via the kidneys and bile. The half-life is about 9h.

Interactions See Table A.57.

Table A.57 Interactions of candesartan

Medications whose plasma levels are altered by candesartan	Pharmacodynamic interactions
Levels increased: lithium	With ACE inhibitors, calcineurin inhibitors, heparins, trimethoprim: increased risk of hyperkalaemia With antihypertensives: increased risk of hypotension With NSAIDs: increased risk of renal impairment

References

Langford RM, Mares J, Novotna A, *et al*. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J Neurol* 2013;**260**(4):984–97.

Nurmikko TJ, Serpell MG, Hoggart B, *et al*. Sativex successfully treats neuropathic pain characterized by allodynia: a randomized, double blind, placebo-controlled clinical trial. *Pain* 2007;**133**(1–3):210–20.

Tronvik E, Stovner L, Helde G, *et al*. Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. *JAMA* 2003;**289**(1):65–9.

Wade DT, Makela PM, House H, *et al*. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. *Mult Scler* 2006;**12**(5):639–45.

Cannabinoids (Sativex®)

The Sativex® formulation contains two active phytocannabinoids—both naturally occurring within *Cannabis sativa* leaves and flowers, from which the product is produced: delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). It was first approved for use in the UK in 2010.

Uses

In the UK

- *Spasticity*: cannibinoids are licensed as adjunctive treatment for moderate to severe spasticity in individuals aged 18 years and older with MS who have not responded adequately to other anti-spasticity therapies and demonstrate clinically significant improvement during an initial trial of therapy.

Cannabinoids are not currently licensed in the USA.

Off-licence uses

- Neuropathic pain in MS.

Presentation

- *Trade names*: Nabiximols® and Sativex®. Generics are not available.
- *Formulations*: Sativex® is available as an oromucosal spray in 5.5 and 10mL vials. This delivers 0.1mL per actuation. Each 0.1mL spray provides a dose of 2.7mg THC and 2.5mg CBD.

Mechanism of drug action

THC mimics the action of endogenous cannabinoids (endocannabinoids), which are released post-synaptically and act upon presynaptic CB1 cannabinoid receptors. CB1 receptors are found throughout the CNS and PNS—activation leads to decreased excitability and inhibition of neurotransmitter release at the presynaptic neuron. In contrast, CBD has negligible direct effect upon CB1 receptors. Its postulated effects are wide-ranging; however, most of its action is probably due to its role as an indirect antagonist of cannabinoid receptors and as a 5-HT1A receptor agonist. It may also modulate the absorption of THC and decrease its breakdown into psychoactive metabolites, thus reducing undesirable psychotropic side effects. These compounds modulate the endocannabinoid system, which has roles in pain sensation, motor learning, and synaptic plasticity.

Toxicity and side effects

- *Common—cardiovascular*: hypotension, palpitations, tachycardia. *Gastrointestinal*: abdominal pain, anorexia, constipation, diarrhoea, glossodynia, hunger, LFT abnormalities, oral candidiasis, stomatitis, taste disturbance, tooth discoloration, xerostomia. *Musculoskeletal*: weakness. *Neurological*: amnesia, attention deficit, confusion, disorientation, dysarthria, headache, insomnia, lethargy, malaise, unsteadiness. *Ophthalmological*: blurred vision. *Psychiatric*: anxiety, depression, euphoria, panic attack, and paranoia. *Renal*: haematuria, UTI.
- *Serious—cardiovascular*: haemodynamic instability, syncope. *Neurological*: falls. *Psychiatric*: psychosis and suicidality. *Urological*: urinary retention.

Contraindications

- *Absolute*: hypersensitivity to cannabinoids or preparation excipients, personal or family history (suspected or confirmed) of schizophrenia, attempted suicide, personality disorder, or other significant psychiatric disorder (other than depression related to MS).
- *Relative*: severe cardiovascular disease, epilepsy, patients with high falls risk, and those with a history of substance abuse.

Uses in special populations

- *Elderly*: elderly patients (up to 90 years old) have been included in clinical trials. They may be at increased risk of CNS side effects, and the anti-spasticity effect may compound the risk of falls.
- *Pregnancy*: no data are available with regard to the use in pregnancy. The manufacturer advises avoidance in pregnancy, unless benefits outweigh risks.
- *Lactation*: contraindicated due to significant excretion of active metabolites into breast milk.

Efficacy

- *Neuropathic pain*: a small placebo-controlled trial of 66 patients with neuropathic pain of various aetiologies showed that Sativex® reduced pain scores and improved patients' well-being. A recent RCT of 339 participants with MS demonstrated that Sativex® had a small, but significant, effect over placebo in improving patients' pain scores (reduction in pain score by 0.79 on a 10-point scale, compared to placebo; $p = 0.038$). Sativex® was not found to be beneficial for treating painful diabetic neuropathy in a recent systematic review.
- *Spasticity*: the first major trial to specifically assess the role of Sativex® in MS-related spasticity was a two-stage open-label study by Wade and colleagues in 2006. A total of 137 patients were followed for a mean of 434 days and demonstrated a clinically significant reduction in subjective spasticity, as measured by visual analogue scale (VAS).

Dosing and monitoring

Dosing

Start with one spray actuation in the evening for the first 2 days of therapy, then two evening sprays for the next 2 days. Thereafter, the dose can be increased by one spray per day, up to a maximum daily total of 12 sprays. Dosing should be biased towards the evening administration, i.e. five sprays in the morning and seven sprays in the evening. Administration without food/fluid is advised to minimize the amount of swallowed drug. Minimum time between sprays is 15min. A trial for 4 weeks is recommended.

Pharmacokinetics and interactions

Pharmacokinetics

Sativex® is absorbed rapidly through the oropharyngeal mucosa, achieving a maximal plasma concentration of THC at 2–4h. Bioavailability is highly variable between patients due to unpredictable proportions of each dose being swallowed (and thus undergoing first-pass metabolism), rather than absorbed mucosally. Metabolism is hepatic, predominantly hydroxylation by CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The main metabolite of THC is the highly psychoactive 11-OH-THC, while the CBD component is primarily metabolized to 7-OH-CBD. Excretion is as metabolites in the faeces and urine. Extensive binding to fatty tissues results in a biphasic elimination half-life of 4h for redistribution into fat and 3–4 days for terminal elimination.

Interactions See Table A.58.

Table A.58 Interactions of cannabinoids (Sativex®)

Medications which alter Sativex® plasma levels	Pharmacodynamic interactions
Levels decreased: CYP3A4 inducers, e.g. rifampicin	**With anticholinergics:** increased risk of tachycardia
Levels increased: CYP2C9 inhibitors, e.g. valproate; CYP3A4 inhibitors, e.g. ketoconazole	**With CNS depressants:** increased sedation **With MAOIs:** increased risk of orthostatic hypotension

Capsaicin

Capsaicin was first marketed in the UK in 2010. It is derived from chilli peppers and is responsible for the burning sensation when chillis come into contact with the skin and mucous membranes. It is effective in the management of neuropathic pain, its main side effect being localized skin irritation.

Uses

Licensed uses

In the UK/USA
(Licensing is the same.)
- *Neuropathic pain*: topical capsaicin (0.075% cream) is licensed for pain relief in painful diabetic neuropathy and post-herpetic neuralgia in adults. The 8% capsaicin patch is licensed for the treatment of peripheral neuropathic pain in non-diabetic patients in adults.

Off-licence uses None.

Presentation

- *Trade names*: Axsain®, Qutenza®, Zacin®.
- *Formulations*: topical capsaicin is available as a cream and high-strength patch. Cream: 0.025% and 0.075%. High-strength patch: 8%.

Mechanism of action

Capsaicin binds its receptor TRPV1, a heat-activated calcium channel, on nociceptive neurons, which opens between temperatures of 37°C and 45°C and is responsible for sensing heat and pain caused by excessive temperatures. Capsaicin causes TRPV1 to open at temperatures <37°C, causing a perceived burning sensation. Prolonged exposure to capsaicin depletes nociceptive neurons of neurotransmitters, particularly substance P, leading to reduced pain transmission and an analgesic effect. This is reversible on removal of capsaicin.

Toxicity and side effects

The main side effects of intense burning and erythema at the application site can be partially reduced by co-administration of lidocaine.
- *Common—cardiovascular*: hypertension. *Dermatological*: abnormal skin odour, bruising, burning sensation, erythema, excoriation, oedema, pruritus, skin dryness, stinging, urticaria, warmth. *Gastrointestinal*: nausea, vomiting. *Neurological*: dizziness, headache, hypoaesthesia, hyperaesthesia, paraesthesiae, peripheral sensory neuropathy. *Respiratory*: bronchitis, cough, nasopharyngitis, sinusitis, throat irritation.

Contraindications

- *Absolute*: broken or irritated skin, as well as known previous hypersensitivity reactions to capsaicin or its irritants.
- *Relative*: none.

No dose adjustment is required in hepatic or renal impairment.

Uses in special populations

- *Elderly*: no dose adjustment required in the elderly.
- *Pregnancy*: there have been no reported side effects when used in pregnancy, although there is limited evidence. Generally recognized as safe.
- *Lactation*: no studies, but generally recognized as safe, as long as capsaicin does not come into contact with the infant's skin. Do not apply capsaicin to the breast.

Efficacy

A recent systematic review assessed the efficacy of high-dose topical capsaicin (8%) in neuropathic pain. Four studies, involving 1272 participants, demonstrated that 8% capsaicin patches produced significant analgesia over 8- and 12-week periods over low-dose capsaicin (0.04%) in patients with post-herpetic neuralgia, with an NNT of 8.8 (95% CI 5.3–26). Two further studies, involving 801 participants, showed small, but significant, benefits in treating painful HIV neuropathy, with one study showing an NNT of 5.8 (95% CI 3.8–12). Results from application of capsaicin cream (0.025% and 0.075%) have been inconsistent. Another recent systematic review concluded that low-dose capsaicin cream shows no therapeutic benefit above that of placebo in treating neuropathic pain.

Dosing and monitoring

Dosing

Apply the cream sparingly to the affected area, 3–4 times/day for 8 weeks, then review. For patches, apply a 60min application of up to four patches. Repeat every 3 months. Before application of a patch, shave and wash the affected area. Handle the patch with nitrile gloves (not latex). The patch can be trimmed to the necessary dimensions before application. Pre-treat the area of affected skin and the surrounding 1–2cm of the skin with a topical anaesthetic.

Routine monitoring None required.

Pharmacokinetics and interactions

Pharmacokinetics

Capsaicin is rapidly absorbed by the skin. The exact amount absorbed is unknown. There is little available information about the pharmacokinetics of topical capsaicin.

Interactions See Table A.59.

Table A.59 Interactions of capsaicin

Pharmacodynamic interactions
With ACE inhibitors: can increase the severity of cough

References

Derry S, Moore RA. Topical capsaicin (low concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* 2012;**9**:CD010111.

Derry S, Rice ASC, Cole P, *et al*. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* 2013;**2**:CD007393.

Carmustine implant

The carmustine implant was first used in the 1990s. It represents a novel approach to bypassing the blood–brain barrier and thus limiting systemic side effects. It is a well-tolerated medication, used as an adjunct to surgery in the management of high-grade gliomas. Plasma levels of carmustine are undetectable, and systemic side effects are rare.

Uses

Licensed uses

In the UK/USA

- *Glioma*: carmustine implants are licensed for use in newly diagnosed high-grade malignant gliomas as an adjunct to surgery and radiation in the management of histologically confirmed recurrent glioblastoma multiforme where surgical resection is indicated in adult patients.

Off-licence uses

- Single brain metastasis, e.g. breast or lung primaries.

Presentation

- *Trade names*: Gliadel® Wafer. Generics are not available.
- *Formulations*: carmustine implants are available as a wafer (1 × 14mm) containing 7.7mg of carmustine, with polifeprosan, a biodegradable co-polymer designed to control carmustine release.

Mechanism of action

Carmustine implants are administered into the lesion site during reductive surgery. Carmustine is a cell cycle non-specific alkylating agent that acts by forming cross-links in both DNA and RNA. This inhibits DNA and protein synthesis. Part of its action may also be mediated by carbamoylation of amino acids.

Toxicity and side effects

Side effects following the use of carmustine implants are, on the whole, consistent with those of patients undergoing craniotomy for malignant gliomas. Systemic side effects, as seen with IV carmustine, are rare.

The main side effects thought to be specific to intralesional administration of implants include: (1) seizures: up to 54% of patients treated with implants for recurrent glioma developed new or worsened seizures in the first 5 post-operative days; (2) brain oedema ~23% vs 19% for implant and placebo, respectively; (3) impaired neurosurgical wound healing occurs in up to 16% of patients, including wound dehiscence, delayed healing, and wound effusions. As a result of this, the likelihood of developing a CSF leak increased from 0.8% to 5% in the implant group, compared to placebo; (4) abscess/meningitis in 4–5% vs 1–6% for implant and placebo, respectively; and (5) obstructive hydrocephalus due to migration of the implant into the ventricles.

Other events that appear to be commoner in trials when carmustine implants are used, compared to placebo implants, include:

- *common—dermatological*: rash. *Endocrine*: hyponatraemia. *Gastrointestinal*: nausea and vomiting. *Haematological*: anaemia. *Neurological*: confusion, fatigue, and headache. *Respiratory*: pneumonia. *Urological*: UTI;
- *serious—respiratory*: pulmonary embolism.

Contraindications

- *Absolute*: previous hypersensitivity to carmustine.
- *Relative*: due to the risk of implant migration into the ventricular system and the potential development of subsequent hydrocephalus, implant insertion into lesional sites communicating with, or in close proximity to, the ventricular system should be avoided.

Dose reduction is not required in hepatic or renal impairment.

Uses in special populations

- *Elderly*: there are no safety or efficacy data comparing use of the implants in those aged >65 years to those aged <65 years.
- *Pregnancy*: no studies are available that have recorded the effects of carmustine implant in pregnancy. Carmustine, when used IV, has a documented teratogenic risk; hence the implant should not be used in pregnancy.
- *Lactation*: it is not known whether carmustine is present in human breast milk. The manufacturer advises against breastfeeding with the carmustine implant.

Efficacy

In the management of newly diagnosed high-grade glioma, a double-blind, placebo-controlled clinical trial demonstrated that the carmustine implant increased median survival from 11.6 to 13.9 months ($p = 0.079$), when used as an adjunct to surgery. Within the context of recurrent glioblastoma, a randomized, double-blind, placebo-controlled trial demonstrated improvement in the 6-month survival rate from 36% to 56% ($p = 0.01$).

Dosing and monitoring

Dosing

For the management of both new-onset high-grade glioma and recurrent glioblastoma, ~7–8 implants are used, depending on cavity size.

Routine monitoring

No additional monitoring is required above that routinely used to detect potential post-operative complications.

Pharmacokinetics and interactions

Pharmacokinetics

The exact pharmacokinetics of the carmustine wafer are poorly understood. Implants release carmustine over a period of 5 days and should degrade completely over 6–8 weeks, provided continuous contact with interstitial fluid. Carmustine delivery to brain interstitial tissues is mediated

by both diffusion and a bulk flow mechanism created by vasogenic oedema (most prominent in the first 3 days post-surgery).

The majority of the carmustine component of the implant is excreted renally, with ~62% of radiolabelled carmustine present in the urine at 7 days. The metabolism of interstitial carmustine is not known. In rabbits with implants, no detectable levels were found in the plasma or CSF, suggesting minimal systemic distribution of carmustine.

Interactions

Interactions with other medications have not been formally evaluated. The localized application and low systemic uptake with the implant suggests there are unlikely to be any significant pharmacokinetic interactions.

References

Attenello FJ, Mukherjee D, Datoo G, *et al*. Use of Gliadel (BCNU) wafer in the surgical treatment of malignant glioma: a 10-year institutional experience. *Ann Surg Oncol* 2008;**15**(10):2887–93.

Brem H, Piantadosi S, Burger PC, *et al*. Placebo-controlled trial of safety and efficacy of intraoperative delivery by biodegradable polymers of chemotherapy for recurrent gliomas. *Lancet* 1995;**345**(8956):1008–12.

Ewand MG, Drem S, Gilbert M, *et al*. Treatment of single brain metastasis with resection, intracavity carmustine polymer wafers, and radiation therapy is safe and provides excellent local control. *Clin Cancer Res* 2007;**13**(12):3637–41.

Clopidogrel

Clopidogrel is a theopyridine class antiplatelet drug that is widely used in the management of cerebrovascular disease. It was first marketed in the UK in the 1990s.

Uses

Licensed uses

In the UK/USA

- *Prevention of stroke*: clopidogrel is licensed for the secondary prevention of thrombotic cerebrovascular disease in patients who have recently suffered ischaemic stroke (UK licensing specifies the ischaemic stroke should be between 7 days and 6 months ago) in individuals aged 18 years and older.

Off-licence uses

- Acute stroke and TIA where aspirin is not tolerated.

Presentation

- *Trade names*: Grepid® and Plavix®. Generics are available.
- *Formulations*: clopidogrel is available in film-coated tablets at 75mg and 300mg doses.

Mechanism of action

Clopidogrel is an irreversible antagonist at adenosine diphosphate (ADP) receptors. Through this action, platelet aggregation and adhesion to collagen, thrombin, fibrinogen, and von Willebrand factor are reduced.

Toxicity and side effects

The side effect profile of clopidogrel is favourable, compared with aspirin, with a slightly higher frequency of rash and diarrhoea, but a slightly lower frequency of gastric upset and gastrointestinal bleeding.

- *Common—gastrointestinal*: abdominal pain, diarrhoea, and dyspepsia. *Haematological*: iron deficiency anaemia. *Neurological*: dizziness, headache.
- *Serious—dermatological*: Stevens–Johnson syndrome, toxic epidermal necrolysis. *Gastrointestinal*: gastrointestinal bleeding, gastric and duodenal ulcers, acute liver failure. *Haematological*: thrombocytopenia, leucopenia, pancytopenia. *Immunological*: allergic reaction. *Respiratory*: interstitial pneumonitis.

Contraindications

- *Absolute*: active peptic ulceration or intracranial haemorrhage; severe hepatic impairment.
- *Relative*: patients deemed to be at a high risk of bleeding. Clopidogrel should be used in caution in patients with renal impairment or mild/moderate hepatic impairment, as there are limited available data for use in these patients.

Uses in special populations

- *Elderly*: the elderly are at a higher risk of gastrointestinal bleeding, and this must be considered when commencing clopidogrel in this population.
- *Pregnancy*: animal studies do not suggest harmful effects to the fetus; however, there is limited experience from use in humans, and hence the manufacturer advises avoidance in pregnancy.
- *Lactation*: clopidogrel is present in mammalian milk; hence the manufacturers advise avoidance in nursing mothers.

Efficacy

The *CAPRIE* trial randomly assigned 19185 patients with either recent stroke, MI, or symptomatic peripheral artery disease to either aspirin (325mg) or clopidogrel (75mg), both OD. The primary endpoint was stroke, MI, or vascular death and was significantly reduced in the cohort treated with clopidogrel (RRR 8.7%, 95% CI 0.3–16.5%). Most of the benefit was observed in patients with peripheral artery disease, and the difference in composite outcome between clopidogrel and aspirin treatment in patients with recent stroke (RRR 0.5% per year) was not significant. However, these are subgroup analyses, and caution must be utilized in their interpretation. The PRoFESS trial showed that clopidogrel monotherapy and aspirin with extended-release dipyridamole resulted in similar rates of recurrent stroke (8.8% vs 9.0%).

Dosing and monitoring

Dosing Start treatment at 75mg od.

Monitoring Monitor FBC in patients deemed at risk of bleeding.

Pharmacokinetics and interactions

Pharmacokinetics

Absorption of clopidogrel is ~50%. Repeated doses of 75mg/day produce substantial inhibition of ADP-induced platelet aggregation from the first day; this increases progressively and reaches a plateau between days 3 and 7 of treatment. At steady state, the average inhibition level observed with a dose of 75mg/day was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued. Clopidogrel is a prodrug. Metabolism is hepatic: 85% by esterases into an inactive metabolite and 15% by several of CYP450 enzymes, including CYP3A4, CYP2C19, CYP1A2, and CYP2B6, into an intermediately active metabolite, which undergoes further metabolism into its strongly active thiol metabolite. Peak plasma levels of the active metabolite are reached at 45min post-dose. After a single oral dose of 75mg, clopidogrel has a half-life of ~6h. Clopidogrel is predominantly eliminated as metabolites, 50% by the renal tract and the rest in faeces.

Poor CYP2C19 metabolizers (14% of Chinese, 4% of Afro-Caribbeans, 2% of Caucasians) have reduced levels of clopidogrel active metabolites.

Studies of the clinical impact of this phenomenon that have been conducted so far are typically small and retrospective in design. They have not been able to clearly demonstrate that poor metabolizers of clopidogrel are associated with increased rates of stroke while on clopidogrel treatment, compared to normal metabolizers, or that alternative antiplatelets are of greater benefit in this group.

Interactions See Table A.60.

Table A.60 Interactions of clopidogrel

Pharmacodynamic interactions
With aspirin, coumarins, dipyridamole, heparins, iloprost, NSAIDs, and prasugrel: increased risk of bleeding
With carbamazepine, chloramphenicol, ciprofloxacin, etravirine, erythromycin, fluconazole, fluoxetine, fluvoxamine, itraconazole, ketoconazole, moclobemide, oxcarbazepine, and voriconazole: possible reduction of antiplatelet effect of clopidogrel
With cimetidine, omeprazole, and esomeprazole: reduction in antiplatelet effect (although current evidence is conflicting)
With coumarins and phenindione: enhancement of anticoagulant effect

Reference

CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**(9038):1329–39.

Cyclophosphamide

This alkylating agent was first synthesized for use as a chemotherapeutic agent in the 1950s. It is currently used in a wide range of inflammatory neurological diseases.

Uses

Licensed uses

In the UK/USA

- There are no licensed neurological uses.

Off-licence uses

- ADEM (severe refractory cases).
- Behçet's.
- MMN with conduction block (refractory cases).
- MG (refractory cases).
- Neurolupus (first-line, acute or chronic).
- NMO (second-line, acute or chronic).
- PM/DM (refractory cases).
- Primary CNS vasculitis (first-line, acute or chronic).
- Sjögren's syndrome.
- Susac's syndrome.
- TM (refractory cases).

Presentation

- *Trade names*: Cytoxan® and Neosar®. Generics are available.
- *Formulations*: cyclophosphamide is available as an oral capsule, an oral tablet (Cytoxan®), or a vial of powder for IV infusion (Cytoxan® and Neosar®). Oral capsule: 25mg and 50mg. Oral tablet: 25mg and 50mg. Vial: 100mg, 200mg, 500mg, 1000mg, and 2000mg.

Mechanism of action

The antineoplastic and immunosuppressant effects of cyclophosphamide are primarily exerted through lymphocyte cytotoxicity. Alkylation and cross-linking of DNA bases in lymphocytes impairs DNA synthesis and transcription, resulting in cell death.

Toxicity and side effects

Acute sterile haemorrhagic cystitis occurs in 10% of patients not co-prescribed mesna (Uromitexan®), an oral antioxidant, which prevents urinary toxicity by interacting with metabolites of cyclophosphamide in the urinary tract.

- *Common—dermatological*: alopecia and rash. *Gastrointestinal*: abdominal pain, anorexia, diarrhoea, nausea, and vomiting.
  Genitourinary: azoospermia and chemical cystitis (in the absence of mesna). *Gynaecological*: amenorrhoea. *Haematological*: leucopenia.
- *Serious—cardiovascular*: arrhythmia, congestive heart failure, myocarditis, and pericarditis. *Gastrointestinal*: hepatic impairment (including veno-occlusive disease). *Genitourinary*: bladder contractures or fibrosis secondary to chemical cystitis (which can be haemorrhagic) and

secondary urothelial malignancy can occur. *Haematological*: bone marrow failure. *Immunological*: anaphylaxis and increased risk of infections and malignancies. *Respiratory*: pneumonitis, pulmonary fibrosis, and pulmonary veno-occlusive disease.

Cyclophosphamide can cause infertility in both men and women. This should be discussed prior to treatment, and oocyte or sperm preserving procedures discussed, as appropriate.

Contraindications

- *Absolute*: hypersensitivity, haemorrhagic cystitis, moderate or severe hepatic impairment (bilirubin >17micromol/L or serum transaminases/ALP >2–3 times the upper limit of normal), and renal impairment (serum creatinine >120micromol/L).
- *Relative*: cyclophosphamide should be used with caution in patients with mild renal or mild hepatic impairment, and dose reductions are necessary.

Use in special populations

- *Elderly*: cyclophosphamide has not been studied in this group, but, in light of an age-related deterioration in hepatic and renal function, cautious use with lower doses is often necessary.
- *Pregnancy*: this drug is teratogenic and should be avoided during, and for 1 year after, therapy. Male patients should use contraception during, and for 6 months following, treatment.
- *Lactation*: breastfeeding should be avoided with this drug.

Efficacy

See relevant conditions in Chapter 6, Inflammatory disorders of the central nervous system.

Dosing and monitoring

Dosing

Dosing regimens vary between indications and between hospitals. We recommend the reader follows local protocols. A typical regimen (CYCLOPS protocol) for central and peripheral vasculitis is given below.

Vasculitis of the nervous system (central or peripheral): 15mg/kg/pulse. The first three pulses are given IV at intervals of 2 weeks. Subsequent doses are given 3-weekly (either 15mg/kg IV or 5mg/kg PO for 3 days). Remission should be achieved within 3 months, with 3 more months of cyclophosphamide after entry into remission. If remission is not achieved, then further pulses can be given at 3-weekly intervals until remission is reached. Remission must be achieved by 9 months, and total duration of therapy should not exceed 12 months. Three months after remission is achieved, switch to a remission maintenance regimen (e.g. azathioprine). Patients aged older than 60 and with an eGFR <30mL/min will need dose reductions.

Monitoring

FBC, and hepatic and renal function should be monitored frequently prior to, and regularly during, treatment. In addition, a minimum urine output of 100mL/h and frequent bladder emptying should be encouraged to avoid cystitis.

Pharmacokinetics and interactions

Pharmacokinetics

The bioavailability of cyclophosphamide is >75%. Serum concentrations peak 1h post-dose. The drug is rapidly converted to its active metabolites, including acrolein and 4-aldophosphamide, in the liver by mixed function oxidases in hepatic microsomes. Metabolites of cyclophosphamide are excreted into the urine. Up to 25% of the parent compound can be found in the urine. The half-life is 3–12h.

Interactions See Table A.61.

Table A.61 Interactions of cyclophosphamide

Medications whose plasma levels are altered by cyclophosphamide	Pharmacodynamic interactions
Decreased levels: digoxin **Increased levels:** suxamethonium	**With clozapine:** there is an increased risk of agranulocytosis **With fluconazole, itraconazole, and pentostatin:** the side effects are increased

Dabigatran

Dabigatran was first marketed in the UK in 2010. It is an effective anticoagulant, which can be used when there is poor INR control, despite compliance with warfarin therapy, or in patients who are allergic to, or unable to tolerate, warfarin.

Uses

Licensed uses

In the UK/USA

- *Prevention of stroke*: dabigatran is licensed to prevent stroke and systemic embolization in people with non-valvular AF in individuals aged 18 years and older. In the UK, individuals need to score at least 1 point on the CHADS2 VASc score.

Off-licence uses

- None.

Presentation

- *Trade names*: Pradaxa®. Generics are not available.
- *Formulations*: dabigatran is available as 110mg and 150mg capsules.

Mechanism of action

Dabigatran is a potent, competitive, reversible direct thrombin inhibitor. Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin, and thrombin-induced platelet aggregation.

Toxicity and side effects

- *Common—dermatological*: pruritus, rash. *Gastrointestinal*: abdominal pain, constipation, diarrhoea, dyspepsia, nausea, vomiting. *Haematological*: anaemia. *Immunological*: allergic reaction. *Neurological*: headaches.
- *Serious—gastrointestinal*: intra-abdominal haemorrhage, hepatitis. *Haematological*: haemorrhage. *Neurological*: intracranial haemorrhage.

Contraindications

- *Absolute*: dabigatran is contraindicated in people with severe renal impairment (CrCl <30mL/min), severe liver disease, particularly if the prothrombin time is already prolonged, active clinically significant bleeding, known severe hypersensitivity reaction to dabigatran, those with mechanical heart valves, organic lesions at risk of bleeding, impairment of haemostasis, those already on alternative anticoagulant medication, and hepatic impairment or liver disease expected to have an impact on survival. Concomitant treatment with systemic ketoconazole, ciclosporin, itraconazole, or tacrolimus is also contraindicated.
- *Relative*: patients deemed to be at high risk of bleeding. In moderate renal impairment (CrCl 30–50mL/min), use a reduced dose of 110mg bd if patients are deemed to be at high risk of bleeding. No dose adjustment is required in mild renal impairment.

Uses in special populations

- *Elderly*: patients have a 31% higher trough concentration if they are aged ≥75 years, compared to subjects aged between 65 and 75 years. Hence, if the thrombotic risk is low and the bleeding risk high, a reduced dose of 110mg bd can be considered, at the clinician's discretion, in those aged 75–80 years. Patients aged ≥80 years should automatically receive this reduced dose.
- *Pregnancy*: toxicity has been demonstrated in animal studies; therefore, it should be avoided, unless essential.
- *Lactation*: no data are available, and thus its use should be avoided.

Efficacy

In the *RE-LY* trial, 18113 patients with non-valvular AF and intermediate risk for thromboembolism (mean CHADS2 score of 2.1) were randomly assigned to receive oral dabigatran at one of two doses (110 or 150mg) bd or warfarin. Dabigatran 110mg met the criteria for non-inferiority, compared to adjusted-dose warfarin (RR 0.90, 95% CI 0.74–1.10), while dabigatran 150mg was significantly more effective than warfarin (RR 0.65, 95% CI 0.52–0.81). The risk of major bleeding was significantly less with dabigatran 110mg than warfarin, and dabigatran 150mg was of equal safety to warfarin.

Dosing and monitoring

Dosing

The recommended daily dose for prevention of stroke in non-valvular AF is 300mg taken as one 150mg capsule bd (reduce dose in elderly, see p. 438).

Monitoring

Dabigatran does not currently require routine anticoagulant monitoring. However, recently released analyses from the RE-LY trial suggest that a one-off or annual measurement of dabigatran plasma levels may reduce the rate of bleeding by 30–40%, without affecting the chances of ischaemic stroke. Whether this becomes routine in the future is as yet unclear. The INR test is unreliable and therefore should not be performed. Diluted thrombin time (dTT), ecarin clotting time (ECT), and activated partial thromboplastin time (aPTT) may provide useful information, but the tests are not standardized, and results should be interpreted with caution. Monitor renal function at least annually, more frequently in the elderly.

Pharmacokinetics and interactions

Pharmacokinetics

After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran by esterase-catalysed hydrolysis. Oral bioavailability of dabigatran is ~6.5%. T_{max} is 0.5–2h. Food co-ingestion delays T_{max} but has no effect on bioavailability. Dabigatran undergoes minimal metabolism to acylglucuronides, which retain pharmacological activity. Eighty-five per cent of dabigatran is eliminated in the urine, predominantly as unchanged drug.

Interactions See Table A.62.

Table A.62 Interactions of dabigatran

Medications which alter dabigatran plasma levels	Pharmacodynamic interactions
Levels decreased: carbamazepine, phenytoin, rifampicin, and St John's Wort **Levels increased:** amiodarone, ciclosporin, dronedrone, ketoconazole, itraconazole, rilpivirine, tacrolimus, telaprevir, and verapamil	**With antiplatelets, anticoagulants, NSAIDs, and SSRIs:** increased risk of bleeding

References

Connolly SJ, Ezekowitz MD, Yusuf S, *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**(12):1139–51.

Connolly SJ, Ezekowitz MD, Yusuf S, *et al*. Newly identified events in the RE-LY trial. *N Engl J Med* 2010;**363**(19):1875–6.

Eikelboom JW, Wallentin L, Conolly SJ, *et al*. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011;**123**(21):2363–72.

Dantrolene

Dantrolene is a skeletal muscle relaxant, first used as a treatment for spasticity in the 1970s. It is now much better known for its use in the treatment of malignant hyperthermia and is generally reserved as a second-line agent in spasticity.

Uses

Licensed uses

In the UK

- *Spasticity*: dantrolene is licensed for the treatment of chronic, severe spasticity in individuals aged 18 years and older.
- *Malignant hyperthermia*: the IV preparation is licensed for the treatment of malignant hyperthermia in individuals aged 18 years and older.

In the USA

- *Spasticity*: dantrolene is licensed for the treatment of chronic spasticity of UMN origin in individuals aged 5 years and older.
- *Malignant hyperthermia*: the IV formulation is licensed for the treatment of malignant hyperthermia in individuals of all ages. PO and IV formulations are also licensed for preoperative/post-operative prevention of malignant hyperthermia in individuals of all ages (IV) and individuals aged 5 years and older (PO).

Off-licence uses

- Treatment of NMS and serotonin syndrome.

Presentation

- *Trade names*: Dantrium®, Dantrium® IV. Generics are not available.
- *Formulations*: dantrolene is available as a capsule and powder for reconstitution as an IV infusion. Capsule: 25mg and 100mg. Powder: 20mg.

Mechanism of action

Dantrolene acts at the level of muscle fibres by blocking the RyR1 channel, through which calcium is released from the sarcoplasmic reticulum. This reduction of free calcium reduces actin–myosin cross-linkage, and thus excitation–contraction coupling, resulting in muscle relaxation.

Toxicity and side effects

- *Common—cardiovascular*: exacerbation of heart failure, hyper-/hypotension, and tachycardia. *Dermatological*: hyperhydrosis, rash. *Gastrointestinal*: abdominal pain, anorexia, constipation, diarrhoea, dysphagia, nausea, vomiting. *Neurological*: dizziness, drowsiness, fever, headache, seizures, speech disturbance. *Ophthalmological*: visual disturbance. *Psychiatric*: confusion, depression, insomnia. *Respiratory*: dyspnoea, pleural effusion, respiratory depression. *Urological*: crystaluria, frequency, haematuria, incontinence, retention.
- *Severe—cardiovascular*: pericarditis has been reported. *Gastrointestinal*: fatal hepatotoxicity has been reported in clinical trials.

This is commoner with females, the over 30s, previous history of hepatic dysfunction, long-term high-dose therapy, and concurrent use of alternative hepatotoxic agents, including tizanidine (co-prescription should be avoided). *Haematological*: aplastic anaemia, neutropenia, and thrombocytopenia have been reported.

Contraindications

- *Absolute*: hypersensitivity to dantrolene, hepatic dysfunction (except for emergencies in the setting of malignant hyperthermia), and acute muscle spasm.
- *Relative*: concomitant calcium channel blockers (potential for profound hyperkalaemia and ventricular fibrillation).

No dosage adjustment is required in renal impairment.

Uses in special populations

- *Elderly*: the elderly may be more susceptible to hepatotoxicity and sedation. Cautious dose titration is recommended.
- *Pregnancy*: embryo toxicity has been observed in animal studies, and thus use in pregnancy is not recommended.
- *Lactation*: dantrolene is excreted into breast milk in potentially significant quantities, so either dantrolene or breastfeeding should be discontinued.

Efficacy

A 2004 systematic review found dantrolene to be superior to placebo for relieving spasticity of various aetiologies in 7 out of 16 small trials, although outcomes measured varied widely. The only available head-to-head data come from three small trials comparing dantrolene to diazepam, in which no difference in efficacy was found. The limited evidence available suggests overall tolerability is broadly comparable to baclofen and tizanidine.

Dosing and monitoring

Dosing

- *Malignant hyperthermia*: administer a rapid IV dose at 1mg/kg; this can be increased until symptoms subside or 10mg/kg has been given. Oral dantrolene can be given at 4–8mg/kg/day in four divided doses for 1–3 days post-crisis to prevent recurrence.
- *Spasticity*: start treatment at 25mg od; after 1 week, increase to 25mg bd, an extra 25mg added to each dose or an extra dosing interval is then added in alternate weeks up to a maximum of 400mg daily in four divided doses.

Routine monitoring

LFTs should be performed at baseline and repeated regularly during the first year. Patients and carers should be educated regarding the signs of early hepatic dysfunction (pruritus, pale stools, dark urine, nausea, vomiting, etc.)

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is 70%. Peak plasma levels occur at 3–6h. Plasma half-life is 6–9h, with plasma concentrations remaining therapeutic for ~5h. There is no significant effect of food on absorption or metabolism. Dantrolene is a CYP3A4 substrate (though not an inducer or inhibitor) and mainly undergoes hydroxylation in the liver to 5-hydroxydantrolene, which has similar efficacy and a longer half-life, compared to the parent compound. Elimination is predominantly renal, primarily as 5-hydroxydantrolene. A small percentage is excreted as unchanged dantrolene.

Interactions See Table A.63.

Table A.63 Interactions of dantrolene

Medications which alter dantrolene plasma levels	Pharmacodynamic interactions
Levels decreased: CYP3A4 inducers, e.g. rifampicin	**With calcium channel blockers (non-dihydropyridine):** hyperkalaemia, reduced cardiac output (avoid combination)
Levels increased: CYP3A4 inhibitors, e.g. ketoconazole	**With CNS depressants:** increased sedation
	With hepatotoxic agents, e.g. tizanidine: increased risk of hepatotoxicity
	With vecuronium: increased risk of neuromuscular block

References

Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. *J Pain Symptom Manage* 2004;**28**(2):140–75.

Krause T, Gerbershagen MU, Fiege M, *et al*. Dantrolene—a review of its pharmacology, therapeutic use and new developments. *Anaesthesia* 2004;**59**(4):364–73.

Shakespeare D, Boggild M, Young CA. Anti-spasticity agents for multiple sclerosis. *Cochrane Database Syst Rev* 2003;**4**:CD001332.

Desmopressin

Desmopressin was first used in the treatment of diabetes insipidus in the 1970s. Today, it is most commonly used in the management of cranial diabetes insipidus, haemophilia, and primary enuresis in children. It can also be used as a second-line therapy in the management of nocturia in patients with MS. Although used in small doses for the latter indication, its use is limited by the potential to develop symptomatic hyponatraemia, and, for this reason, it should be avoided in patients with fluid overload syndromes, e.g. heart failure.

Uses

Licensed uses

In the UK

Desmopressin intranasal solution is licensed for the treatment of nocturia associated with MS where other treatments have failed in individuals aged up to 65 years of age.

In the USA

Desmopressin is not licensed for nocturia associated with MS.

Off-licence uses

- None.

Presentation

Only the intranasal solution is licensed for use in the management of nocturnal enuresis associated with MS in the UK, although other formulations, most commonly tablets, are used off-licence for this indication. Solutions for IV injections are used for other indications. Only the nasal and tablet forms are discussed further below.

- *Trade names*: DDAVP®, DDAVP Rhinal tube®, DesmoMelt®, Desmotabs®, and Desmospray®. Generics are available.
- *Formulations*: desmopressin is available as a nasal solution, a nasal spray, a standard tablet, and a sublingual tablet. Nasal solution: 2.5mL and 5mL vials at 0.01%. Nasal spray: 10 micrograms/metered spray. Standard tablet: 100 micrograms and 200 micrograms. Sublingual tablet: 60 micrograms, 120 micrograms, and 240 micrograms.

Mechanism of action

Desmopressin is a structural analogue of vasopressin (ADH), a nanopeptide produced by the pituitary gland with vasopressor and antidiuretic effects. Its molecular structure differs slightly from vasopressin, meaning that there is a loss of affinity for vasopressin type 1 receptors (V1) and a relative increase in affinity for V2 receptors. V1 receptors are predominantly responsible for vasopressor activity, and V2 receptors for antidiuretic activity, meaning that desmopressin has 12 times greater antidiuretic activity, and 200 times less vasopressor activity, than endogenous vasopressin. The antidiuretic effect of desmopressin through the V1 receptor is mediated by increased permeability of the renal collecting ducts, thereby increasing reabsorption of water.

Toxicity and side effects

- *Common—cardiovascular*: fluid retention. *Gastrointestinal*: abdominal pain, nausea, and vomiting. *Neurology*: headache.
- *Serious—dermatological*: severe allergic reactions.
  Endocrine: hyponatraemia, which can be severe and result in convulsions.

Contraindications

- *Absolute*: heart failure and other fluid overload syndromes requiring diuretics, psychogenic polydipsia, and polydipsia associated with alcohol dependence.
- *Relative*: use with caution in patients with cardiovascular disease, cystic fibrosis, hypertension, and hyponatraemia and those at risk of raised ICP, and avoid for nocturnal enuresis in the elderly (>65 years of age). Use with caution in patients with renal failure, and avoid if CrCl is <50mL/min. No precautions or dose adjustments are routinely recommended in hepatic impairment.

Uses in special populations

- *Elderly*: avoid in individuals aged >65 years, due to age-related increase in the risk of cardiovascular and renal disease.
- *Pregnancy*: animal studies and one low-quality epidemiological study of desmopressin use in pregnant women with diabetes insipidus have not shown an increased risk of teratogenicity with use of the drug; however, a few case studies have documented congenital anomalies in patients on desmopressin therapy. There may be an increased risk of pre-eclampsia; hence the manufacturer advises to avoid use, where possible.
- *Lactation*: it is not known if desmopressin is present in breast milk or what effects its presence could have on the newborn; hence desmopressin should be avoided or used with caution in nursing mothers.

Efficacy

Three small RCTs have investigated the use of desmopressin in the management of nocturia in patients with MS. All three trials demonstrated a significant reduction in the frequency of voiding and improved sleep, although there was no significant reduction in episodes of incontinence. In the oldest trial, nocturia was reduced from an average of 2.55 voids per night to 1.28 with desmopressin vs 2.01 with placebo (p <0.01), and, in the most recent trial, the maximum hours of uninterrupted sleep increased from 3.74 to 5.77 with desmopressin treatment. Reports compiled by the Medicines and Healthcare Products Regulatory Agency (MHRA) in 2007 suggested that the nasal spray may be associated with a higher rate of hyponatraemia than the oral formulations, and hence many prescribers will opt to first try oral desmopressin.

Dosing and monitoring

Dosing

- Nasal solution: 10–20 micrograms. Standard tablet: 100–200 micrograms. Sublingual tablet: 60–120 micrograms. The dose should be taken at bed time, and fluid intake should be limited to a minimum from 1h before to 8h after dosing. Do not repeat dosing within 24h.

Routine monitoring No routine monitoring required.

Pharmacokinetics and interactions

Pharmacokinetics

The average bioavailability and T_{max} of intranasal, oral, and sublingual routes are ~10% and 1h, 0.08–0.16% and 1.5–2h, and 0.25% and 0.5–2h, respectively, although this is highly variable between patients. The route of metabolism is not clear, although *in vitro* experiments suggest it is unlikely to be hepatic. The half-life for all routes is ~3h. Elimination is predominantly renal.

Interactions See Table A.64.

Table A.64 Interactions of desmopressin

Medications which alter plasma levels of desmopressin	Pharmacodynamic interactions
Levels increased: loperamide	**With NSAIDs:** may increase the risk of fluid retention **With conivaptan, demeclocycline, and lithium:** may reduce the effect of desmopressin

References

Hilton P, Hertogs K, Stanton SL. The use of desmopressin (DDAVP) for nocturia in women with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1983;**46**(9):854–5.

Valiquette G, Herbert J, Maede-D'Alisera P. Desmopressin in the management of nocturia in patients with multiple sclerosis. *Arch Neurol* 1996;**53**(12):1270–5. .

Dexamfetamine (dexamphetamine) sulfate

Dexamfetamine was first marketed in the UK in the 1930s. It is a centrally acting stimulant drug used as a second-line agent in the treatment of narcolepsy if modafinil is not effective. Older studies have demonstrated its effectiveness at promoting wakefulness, although its behavioural and cardiovascular side effects, in addition to its potential as a drug of abuse, limit its wider use.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- *Narcolepsy*: dexamfetamine is licensed for use in the treatment of narcolepsy in individuals aged 3 years and older.

Off-licence uses

- None.

Presentation

- *Trade names*: Dexedrine®, Dextrostat®, Liquadd®, and Procentra®. Generics are available.
- *Formulations*: dexamfetamine is available as an oral solution, standard tablets, and sustained-release capsules. Oral solution: 5mg/5mL. Standard tablets: 5mg and 10mg. Sustained-release capsules: 5mg, 10mg, and 15mg.

Mechanism of action

Dexamfetamine sulfate is a non-catecholamine, sympathomimetic amine which acts as a central stimulant by promoting the release of catecholamines and, to a lesser extent, by preventing their reuptake into presynaptic nerve terminals by competitive inhibition.

Toxicity and side effects

- *Common—gastrointestinal*: abdominal pain, anorexia, nausea, unpleasant taste, vomiting, and weight loss. *Neurological*: fatigue and insomnia. *Psychiatric*: anxiety, behavioural disturbance, e.g. aggression and elation.
- *Serious—cardiovascular*: cardiomyopathy and MI can occur. *Gastrointestinal*: ischaemic colitis. *Musculoskeletal*: rhabdomyolysis. *Ophthalmological*: rarely angle-closure glaucoma. *Neurological*: cerebral vasculitis, NMS, movement disorders, including tics, seizures, and stroke. *Psychiatric*: psychosis.

Contraindications

- *Absolute*: hypersensitivity to dexamfetamine or its excipients. Patients with advanced atherosclerosis, symptomatic cardiovascular disease, cardiomyopathy, or moderate to severe hypertension. Patients with Gilles de la Tourette syndrome or other tic disorders, glaucoma,

hyperthyroidism, or porphyria. Dexamfetamine is also a potential drug of abuse and should be avoided in patients with a history of alcohol or drug abuse. It should also be avoided during, or for 14 days after, treatment with an MAOI. Tablets contain lactose and sucrose, and hence patients with hereditary problems of lactose/sucrose metabolism should avoid dexamfetamine.

- *Relative*: use with caution in patients on guanethidine, and those with mild hypertension, family history of tic disorders, renal impairment, or unstable personalities. Dexamfetamine lowers the seizure threshold; hence use with caution in epilepsy. Dexamfetamine causes weight loss; hence use with caution in anorexia nervosa. No alteration in dose is given in the product literature with regard to hepatic impairment; however, dexamfetamine is extensively hepatically metabolized and hence should be used with caution in patients with hepatic dysfunction.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function, and have a higher risk of dexamfetamine exacerbating pre-existing cardiovascular and cerebrovascular disorders. Hence half of the adult dose should be used in those >65 years of age.
- *Pregnancy*: evidence is based on illicit exposure and animal studies. Use in pregnancy is contraindicated, as it may lead to increased risk of premature death, low birthweight, neonatal withdrawal syndromes, and potentially behavioural disorders in childhood.
- *Lactation*: the exact amount of dexamfetamine present in human breast milk is unknown. Dexamfetamine may reduce breast milk production, and transmission to a nursing infant is associated with behavioural disturbance. Mothers using dexamfetamine should use alternative feeding methods.

Efficacy

There is little high-quality evidence looking at the effects of dexamfetamine in the management of narcolepsy. Older studies investigated the effects of medications on multiple sleep latency testing (i.e. how fast one falls asleep in a quiet environment—as a measure of excessive daytime sleepiness). One survey demonstrated that use of dexamfetamine resulted in a significant increase in sleep latency from 35% to 70% of normal ($p = 0.01$).

Dosing and monitoring

Dosing

For the treatment of narcolepsy, age >12 years: start treatment at 10mg in divided doses (first dose on waking and further doses at 4–6h intervals). This can be increased by 10mg at weekly intervals, depending on side effects, up to a maximum of 60mg.

Routine monitoring

Assess the BP and cardiovascular risk, and consider an ECG at baseline. Then monitor the BP and cardiovascular risk profile on a regular basis, while on treatment

Pharmacokinetics and interactions

Pharmacokinetics

Knowledge of the pharmacokinetics of dexamfetamine is limited; oral bioavailability of dexamfetamine is >75%. Peak plasma concentrations are reached at different time points, depending on the formulations used: standard tablets at ~2h and sustained-release tablets at ~8h. Thirty to 45% is metabolized hepatically, while the rest is excreted unchanged by the kidneys. The half-life in adults is 10–13h, although this can be enhanced with acidic urine.

Interactions See Table A.65.

Table A.65 Interactions of dexamfetamine

Medications which alter dexamfetamine plasma levels	Medications whose plasma levels are altered by dexamfetamine	Pharmacodynamic interactions
Levels decreased: gastrointestinal acidifying agents (e.g. fruit juices) and urinary acidifying agents (e.g. ammonium chloride) **Levels increased:** gastrointestinal alkalizing agents (e.g. sodium bicarbonate) and urinary alkalizing agents (e.g. acetazolamide, some thiazides)	**Levels decreased:** ethosuximide, phenobarbital, and phenytoin **Levels increased:** corticosteroids	**With adrenergic blockers and antihypertensives:** effects inhibited by dexamfetamine **With catecholamines, MAOIs, and TCAs:** increased cardiovascular side effects **With lithium and typical antipsychotics:** inhibition of central stimulatory effects of amphetamines

References

Mitler MM, Hajdukovic RM. Relative efficacy of drugs for the treatment of sleepiness in narcolepsy. *Sleep* 1991;**14**(3):218–20.

Mitler MM, Hajdukovic RM, Erman M, Koziol JA. Narcolepsy. *J Clin Neurophysiol* 1990;**7**(1):93–118.

Morgenthaler TI, Kapur VK, Brown T, *et al*; Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep* 2007;**30**(12):1705–11.

Diclofenamide

Diclofenamide was approved for use in 1958 in the treatment of glaucoma. It has found use more recently as prophylactic treatment for hyperkalaemic and hypokalaemic periodic paralyses.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- There are no licensed neurological uses.

Off-licence uses

- Prophylaxis of attacks in hyper-/hypokalaemic periodic paralyses.

Presentation

- *Trade name*: Daranide®. Generics are available.
- *Formulation*: diclofenamide is available as a 50mg tablet.

Mechanism of action

Diclofenamide is a carbonic anhydrase inhibitor with pharmacological properties similar to those of acetazolamide. The mechanism of action of this class of medications in the periodic paralyses is unclear, but animal studies have shown that, independent to its inhibition of carbonic anhydrase, diclofenamide can open calcium-activated potassium channels to relieve weakness.

Toxicity and side effects

- *Common—dermatological*: pruritus, skin rash. *Gastrointestinal*: anorexia, diarrhoea, nausea, and vomiting. *Neurological*: drowsiness, paraesthesiae.

Contraindications

- *Absolute*: hepatic insufficiency, renal failure, adrenocortical insufficiency, hyperchloraemic acidosis, severe obstructive airways disease.

Use in special populations

- *Elderly*: diclofenamide should be used with caution, as age-related renal impairment increases the risk of metabolic acidosis.
- *Pregnancy*: diclofenamide has been shown to be teratogenic at high doses in animal models; there are no safety data in human studies. It should be avoided in women of childbearing age and in pregnancy, unless potential benefits outweigh risks.
- *Lactation*: it is not known whether diclofenamide is excreted into human breast milk; the manufacturer advises caution in breastfeeding mothers.

Efficacy

Diclofenamide is effective for the prevention of episodic attacks in periodic paralysis, significantly reducing the frequency and severity of attacks in a combined cohort of hypokalaemic periodic paralysis and hyperkalaemic periodic paralysis by a mean of −1.4 (95% CI −2.97 to 0.17) and −3.5 (−6.38 to −0.62), respectively. There is insufficient evidence to inform whether acetazolamide or diclofenamide is more efficacious for this indication. No established guidelines currently exist for the prophylaxis of attacks of periodic paralysis and whether treatment with carbonic anhydrase inhibitors reduces the risk of developing permanent myopathy later in the natural history of the disease.

Dosing and monitoring

Dosing Commence at 50mg bd.

Monitoring A subgroup of patients may suffer from increased periodic paralysis attack frequency with diclofenamide; therefore, regular clinical review is recommended.

Pharmacokinetics and interactions

Pharmacokinetics

The pharmacokinetics of diclofenamide are poorly described. Expert opinion suggests they are similar to those of acetazolamide (see Acetazolamide, pp. 375–7).

Interactions See Table A.66.

Table A.66 Interactions of diclofenamide

Pharmacodynamic interactions
With phenobarbital or phenytoin: increased risk of osteomalacia
With furosemide and steroids: increased likelihood of diclofenamide side effects
With high-dose aspirin (>300mg/day): risk of anorexia, coma, lethargy, and tachypnoea

Reference

Sansone V, Meola G, Links TP, *et al*. Treatment for periodic paralysis. *Cochrane Database Syst Rev* 2008;1:CD005045.

Dimethyl fumarate

Dimethyl fumarate, previously known as BG-12, was initially used in the treatment of psoriasis. It is the third oral disease-modifying agent used for the treatment of MS. It was licensed for use in the UK in 2014.

Uses

Licensed uses

In the UK/USA

- *MS*: dimethyl fumarate is licensed for relapsing forms of MS in the USA, and RRMS in the UK.

Presentation

- *Trade name*: Tecfidera®. Generics are not available.
- *Formulation*: delayed-release capsule: 120mg or 240mg.

Mechanism of action

Dimethyl fumarate is a fumaric acid ester that has been shown to activate the nuclear factor (erythroid-derived 2)-like 2 or Nrf2 pathway, a pathway involved in the cellular response to oxidative stress, but the exact mechanism of action of this drug is unclear. Studies in MS and prior to this, in the management of psoriasis, have demonstrated immunomodulatory properties, including a reduction in TH1 and TH17 cytokine profiles and reduced circulating levels of lymphocytes.

Toxicity and side effects

- *Common—dermatological*: erythema, flushing (in a third, severe enough to require discontinuation in 3%—Aspirin 75mg before taking the medication may help), pruritus, and rash. *Gastrointestinal*: abdominal pain, deranged LFTs, diarrhoea, dyspepsia, gastritis, gastroenteritis, nausea, and vomiting (GI symptoms often settle and can be minimised by eating fat and protein rich foods before taking the medication). *Genitourinary*: ketonuria and proteinuria. *Haematological*: lymphopaenia ($<0.5 \times 10^9$/L in 6%—these patients are probably at higher risk of PML). *Neurological*: paraesthesiae.
- *Serious—dermatological*: generalized erythema. Neurological: PML has been described although for the most part in patients with low lymphocyte counts.

Contraindications

- *Absolute*: hypersensitivity.
- *Relative*: this drug has not been studied in renal or hepatic impairment and should be used with caution in these patients.

Use in special populations

- *Elderly*: this drug has not been studied in the elderly, but there is no theoretical reason to adjust doses.
- *Pregnancy*: animal studies have shown teratogenicity, and active contraception should be used during treatment.
- *Lactation*: there are no studies on the safety of breastfeeding, and this should therefore be avoided.

Efficacy

For the licensed 240mg bd dose, both the DEFINE (a dose comparison RCT investigating dimethyl fumarate vs placebo) and CONFIRM (Comparator and an Oral Fumarate in Relapsing–Remitting Multiple Sclerosis—an RCT investigating dimethyl fumarate vs glatiramer) studies demonstrated a significant reduction in the proportion of patients relapsing at 2 years, corresponding to a 49% (p <0.0001) relative risk reduction, compared with placebo (DEFINE). The reduction in ARR was 53% (DEFINE) and 44% (CONFIRM) vs placebo. In comparison, glatiramer acetate reduced the ARR by 29%.

The risk of confirmed EDSS progression sustained for 3 months at 2 years was reduced by 38% (p = 0.005) in DEFINE and by 21% (p = 0.25, not significant) in CONFIRM, compared with placebo. In addition, the inflammatory activity on MRI was significantly reduced in both studies, with >70% reduction in T2 and gadolinium-enhancing lesions and >57% reduction in T1 lesions (p <0.0001 for all values) in both studies, compared with placebo.

Dosing and monitoring

Dosing

Start treatment at 120mg bd for 7 days. This is then increased to a usual maintenance dose of 240mg bd.

Routine monitoring

An FBC should be checked prior to initiation and then three monthly, if lymphocytes drop to very low levels for more than 6 months then consider stopping. A baseline MRI should be performed within 3 months of starting treatment to be used as a reference in case symptoms suggestive of PML arise.

Pharmacokinetics and interactions

Pharmacokinetics

The drug undergoes rapid pre-systemic hydrolysis in the gastrointestinal tract following oral administration. This converts the drug to the active monomethyl fumarate, which reaches maximal plasma concentrations in 2–2.5h. This is unaffected by co-ingestion with food. Plasma protein binding accounts for 27–45% of the distribution. The drug is metabolized by the tricarboxylic acid cycle and primarily eliminated by expiration as carbon dioxide. Hepatic and renal excretion accounts for 0.9% and 15.5% of elimination, respectively. The terminal half-life of monomethyl fumarate is ~1h.

Interactions None.

References

Fox RJ, Miller DH, Phillips JT, *et al.*; CONFIRM Study Investigators. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med* 2012;**367**(12):1087–97.

Gold R, Kappos L, Arnold DL, *et al.*; DEFINE Study Investigators. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012;**367**(12):1098–107.

Dipyridamole (modified-release)

Dipyridamole is an antiplatelet drug with additional activity as a non-nitrate coronary artery vasodilator. It was first used in clinical practice in the 1980s. It is now a second-line drug in the management of ischaemic stroke and TIA.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- *Prevention of stroke*: modified-release dipyridamole is licensed for the secondary prevention of ischaemic stroke and TIAs in individuals aged 16 years and older.

Off-licence uses

- Acute stroke and TIA where aspirin and clopidogrel are not tolerated.

Presentation

Dipyridamole MR is available both alone and in combination with low-dose aspirin (25mg).

- *Trade names*: Asasantin Retard® (in combination with aspirin) and Persantin Retard®. Generics of the modified-release form are not available.
- *Formulations*: Asasantin Retard® is available as a 225mg capsule. Persantin Retard® is available as a 200mg capsule.

Mechanism of action

Dipyridamole has dual action as both an adenosine uptake inhibitor and a phosphodiesterase inhibitor; by prevention of uptake of adenosine by red blood cells, platelets, and endothelial cells, it increases extracellular adenosine, which both inhibits platelet activation and promotes arteriodilatation via the P1 receptor. Its activity as a phosphodiesterase inhibitor results in an additional vasodilatory effect.

Toxicity and side effects

- *Common—cardiovascular*: hot flushes, hypotension, tachycardia, and worsening symptoms of coronary artery disease. *Gastrointestinal*: abdominal pain, diarrhoea, and dyspepsia. *Neurological*: dizziness, headache, migraine, and risk of exacerbation of weakness in MG.
- *Serious—cardiovascular*: ventricular arrhythmia and MI. *Gastrointestinal*: gastrointestinal bleeding. *Respiratory*: bronchospasm.

Contraindications

(If using Asasantin Retard®, see Aspirin, pp. 396–8.

- *Absolute*: hypersensitivity to the product.
- *Relative*: use with caution in patients with severe coronary artery disease, left ventricular outflow obstruction, or haemodynamic instability (e.g. decompensated heart failure). No dosing adjustments are required in renal impairment or hepatic impairment, unless there are clinical signs of liver failure, in which case dipyridamole should be avoided, as there is no evidence for this patient group.

Uses in special populations

- *Elderly*: plasma concentrations are 30% higher in this population; hence use with caution, as this population may be at increased risk of bleeding and myocardial ischaemia.
- *Pregnancy*: no adverse effects have been identified from animal studies. However, there are no controlled studies in humans. The manufacturer recommends that dipyridamole should be avoided, particularly in the first trimester.
- *Lactation*: small amounts are present in breast milk; hence dipyridamole should be used with caution in nursing mothers.

Efficacy

The ESPS-2 trial randomly assigned 6602 patients with a recent TIA or ischaemic stroke into either *dipyridamole* monotherapy, *aspirin* monotherapy, a combination of aspirin plus extended-release dipyridamole given bd, or placebo. An independent and significant benefit for stroke risk reduction was observed for both extended-release dipyridamole monotherapy and aspirin monotherapy, compared with placebo ($p < \text{or} = -0.001$). The benefit of the combination *aspirin with extended-release dipyridamole* was significantly greater still than the two components alone. This effect was confirmed in the ESPRIT trial where the composite primary outcome (death from all vascular causes, non-fatal stroke, non-fatal MI, or major bleeding complications) was significantly less frequent in the aspirin plus dipyridamole group than the aspirin alone group after 3.5 years (13% vs 16%) (hazard ratio 0.80, 95% CI 0.66–0.98; absolute risk reduction 1.0% per year, 95% CI 0.1–1.8). The PRoFESS trial showed that *clopidogrel* monotherapy and *aspirin with extended-release dipyridamole* have similar risks and benefits for secondary stroke prevention (8.8% vs 9.0%).

Dosing and monitoring

Dosing

For the secondary prevention of ischaemic stroke and TIAs: 200mg bd, preferably with meals.

Monitoring FBC monitoring should be considered in patients deemed at higher risk of bleeding.

Pharmacokinetics and interactions

Pharmacokinetics

Data given are for dipyridamole MR alone (if giving combination aspirin and dipyridamole therapy, see Aspirin, pp. 396–8). Bioavailability is ~70%, due to first-pass metabolism. Peak plasma concentrations occur at 2–3h after administration. Food co-ingestion has no effect on bioavailability or T_{max}. ~98% of dipyridamole is protein-bound. Steady state occurs at 2 days. Metabolism is predominantly hepatic by conjugation with glucuronic acid to form pharmacologically inactive metabolites: a monoglucuronide and small amounts of a diglucuronide. Ninety-five per cent of these metabolites are excreted into bile. The half-life for conversion of dipyridamole to its metabolites is 2–3h. The elimination half-life for the metabolites is ~15h.

Interactions See Table A.67.

Table A.67 Interactions of dipyridamole

Medications which alter dipyridamole plasma levels	Pharmacodynamic interactions
Levels decreased: antacids	**Adenosine:** dipyridamole enhances and extends the effects of adenosine **Antiplatelets, coumarins, NSAIDs, and phenindione:** increased risk of bleeding **Fludarabine:** dipyridamole may reduce effects of fludarabine

References

Diener HC, Cunha L, Forbes C, *et al*. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996;**143**(1–2):1–13.

ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet* 2006; **367**(9523):1665–73.

Sacco RL, Diener HC, Yusuf S, *et al*. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008;**359**(12):1238–51.

Fampridine (4-aminopyridine)

Fampridine, or dalfampridine, is a voltage-gated potassium channel blocker that is used for symptomatic treatment in MS. It can also be used off-licence for the management of nystagmus and episodic ataxia.

Uses

Licensed uses

In the UK/USA

- *MS*: fampridine is approved to increase walking speed in all forms of MS in patients aged 18 years and older. In the UK, this requires patients to have an EDSS of 4–7.

Off-licence uses

- DBN and EA2.

Presentation

- *Trade names*: Ampyra® and Fampyra®. Generics are not available.
- *Formulation*: modified-release oral tablet: 10mg.

Mechanism of action

Fampridine prolongs presynaptic cell membrane depolarization by blockade of presynaptic voltage-gated potassium channels. This increases the influx of calcium into nerve endings and facilitates exocytosis of acetylcholine-containing vesicles, thereby increasing the speed of action potential conduction. This is thought to increase walking speed in MS, while, in DBN, this mechanism is thought to increase the activity of Purkinje cells in the cerebellum, thereby increasing their inhibitory control of deep cerebellar and vestibular nuclei and ultimately reducing oscillopsia.

Toxicity and side effects

- *Common—gastrointestinal*: constipation, dyspepsia, nausea, and vomiting. *Genitourinary*: UTI. *Musculoskeletal*: back pain. *Neurological*: dizziness, headache, paraesthesiae, and tremor. *Psychiatric*: anxiety and insomnia. *Respiratory*: nasopharyngitis and pharyngolaryngeal pain.
- *Serious—immunological*: anaphylaxis. *Neurological*: seizures.

Contraindications

- *Absolute*: hypersensitivity, seizures, renal impairment (CrCl <80mL/min), and concurrent use of other forms of 4-AP.
- *Relative*: no dose adjustment is required in patients with hepatic impairment. Fampridine should be used with caution in patients with arrhythmias or conduction blocks, as there are limited safety data in these patients.

Use in special populations

- *Elderly*: this drug has not been studied in the elderly, but renal function should be checked prior to initiation and during treatment in this group.
- *Pregnancy*: animal studies have shown teratogenicity, and this drug should not be used during pregnancy.
- *Lactation*: breastfeeding should be avoided.

Efficacy

- *EA2*: a double-blind, randomized, placebo-controlled cross-over trial (n = 10) of 4-AP (5mg tds for 2–3 months, with 1-month washout) in EA2 found 4-AP significantly reduced the frequency and duration of attacks (median monthly frequency—4-AP: 1.65, placebo: 6.50 (p = 0.03); duration—4-AP: 4.45h, placebo: 13.65h (p = 0.08)) and improved quality of life, as reported by Vestibular Disorders Activities of Daily Living Scale, which showed a decrease from 6.00 to 1.50 (p = 0.02) with 4-AP treatment.
- *MS*: a 40% responder rate in a timed 25ft walk has been shown with fampridine in placebo-controlled trials of relapsing–remitting and progressive MS. Responders demonstrated a >20% increase in speed of timed walk.

Dosing and monitoring

Dosing

- *Nystagmus*: an observed test dose is often given first where patients are given either the medication or a placebo, and then the degree of nystagmus, gait, and dynamic visual acuity are assessed pre- and post-dosing. If the test dose is successful, then start treatment at 10mg od, and increase by 10mg every 1–2 weeks, as required/tolerated, up to 10mg tds.
- *MS*: start treatment at 10mg bd. The response to treatment should be assessed using a timed 25ft walking test that is performed before initiation and after 2 weeks. The drug should be discontinued at 2 weeks if there is no improvement. If deterioration in walking later develops, then the drug should be withdrawn, and the response to treatment should be reassessed with a further 2-week trial.

Routine monitoring Perform an ECG at baseline. Some centres may use cardiac monitoring during the first test dose to assess for the presence of arrhythmia.

Pharmacokinetics and interactions

Pharmacokinetics

The absolute bioavailability is not known, and the relative bioavailability is 96%, compared to the aqueous oral solution. Absorption is not affected by co-ingestion of food. Fampridine is 97–99% unbound from plasma proteins. Fampridine undergoes a minimal amount of hepatic metabolism; CYP2E1 hydroxylates fampridine to 3-hydroxy-4-AP. The terminal elimination half-life is 5.2–6.5h, and elimination is nearly complete at 24h; 95.9% is excreted in the urine, and 90.3% of this is unaltered drug.

Interactions See Table A.68.

Table A.68 Interactions of fampridine

Pharmacodynamic interactions
With cimetidine: the manufacturers advise against concomitant use

References

Claassen J, Teufel J, Kalla R, Spiegel R, Strupp M. Effects of dalfampridine on attacks in patients with episodic ataxia type 2: an observational study. *J Neurol* 2013;**260**(2):668–9.

Goodman AD, Brown TR, Edwards KR, *et al.*; MSF204 Investigators. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Ann Neurol* 2010;**68**(4):494–502.

Strupp M, Kalla R, Claassen J, *et al*. A randomized trial of 4-aminopyridine in EA2 and related familial episodic ataxias. *Neurology* 2011;**77**(3):269–75.

Felbamate

Felbamate was originally developed in the 1950s as a potential anxiolytic. It was only 30 years later that research on stroke patients found it demonstrated antiepileptic properties. In the USA, it is strictly a second-line agent. It has been associated with the rare, but severe, side effects of aplastic anaemia and hepatic failure, and this has limited its wider use in the treatment of epilepsy.

Uses

Licensed uses

In the USA

- *Epilepsy*: felbamate is licensed as monotherapy or as an adjunct for the treatment of focal seizures with or without secondary generalization in adults (14 years of age and older) and for the treatment of focal-onset and generalized seizures associated with LGS in children aged 2–14 years old. It is not licensed as a first-line therapy and should only be used in patients failing to respond to alternative AEDs.

Felbamate is not licensed for use in the UK.

Off-licence uses

- Absence seizures.

Presentation

- *Trade names*: Felbatol®. Generics are not available.
- *Formulations*: felbamate is available as an oral suspension and as a scored tablet. Oral suspension: 600mg/5mL. Tablet: 400mg and 600mg.

Mechanism of action

The exact mechanism of action of felbamate has not been fully determined. It has several actions, including: (1) channel-blocking activity via both NMDA and non-NMDA subunits of glutamate receptors; (2) inhibition of voltage-gated sodium channels; (3) barbiturate-like modulation of GABA receptors; (4) inhibition of glutamatergic neurotransmission via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptors.

Toxicity and side effects

- *Common—gastrointestinal*: anorexia, dyspepsia, and nausea, which can result in a temporary weight loss in >50% of patients. *Neurological*: diplopia, dizziness, headache, insomnia, and irritability.
- *Serious—gastrointestinal*: fulminant hepatic failure in 1/7000 to 1/22 000, fatal in 50%. *Haematological*: rarely, aplastic anaemia has been described at an estimated incidence of 1/5000 to 1/20 000, with a mortality rate of 40%. The incidence is commoner in individuals who: (1) are over 18 years of age; (2) are female; (3) have a current or previous history of blood dyscrasia; (4) are being treated with multiple AEDs; and (5) have clinical/serological evidence of an immune disorder. Serious side effects usually occur in the first 6 months of treatment. They are rare after 18 months.

Contraindications

- *Absolute*: known hypersensitivity to felbamate, its excipients, or other carbamates; hepatic dysfunction and blood dyscrasia.
- *Relative*: 50% of felbamate is excreted renally; hence lower doses are required in renal impairment.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function, and benefit from lower dosing regimens.
- *Pregnancy*: animal trials have shown some teratogenic effects; there have been no studies of teratogenicity in humans. Use in pregnancy involves weighing up the potential benefits and side effects. There are no available data on the pharmacokinetics of felbamate during pregnancy.
- *Lactation*: felbamate has been detected in breast milk; it is not known at what concentrations. Breastfeeding should be avoided if possible. If used, infants should be monitored for potential side effects. They should be switched to alternative methods of feeding if these are identified.

Efficacy

Several small RCTs carried out in the early 1990s demonstrated that, when used as monotherapy in uncontrolled focal epilepsy, >50% of patients had reduced seizure frequency. The adverse effect profile of felbamate has meant that few further trials have been undertaken.

Dosing and monitoring

Dosing

For the treatment of epilepsy, age >12 years: start treatment at 600mg bd. This can be increased by 600mg bd on a weekly basis. In adults, doses of up to 6000mg/day have been used.

Routine monitoring FBC and LFTs should be done at baseline, 1 month, and then every 3 months that treatment is continued.

Therapeutic drug monitoring Optimum seizure control when used in monotherapy occurs at plasma concentrations of 30–60mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is ~90%. T_{max} occurs at 3–5h. The half-life is 13–25h. Less than 25% of felbamate is bound to plasma protein. Fifty per cent of felbamate is metabolized by the liver; 95% of the dose is eliminated by the renal system as metabolites and the unchanged medication.

Interactions See Table A.69.

Table A.69 Interactions of felbamate

Medications which alter felbamate plasma levels	Medications whose plasma levels are altered by felbamate
Levels decreased: carbamazepine and phenytoin	**Levels decreased:** carbamazepine, vigabatrin, and warfarin
Levels increased: gabapentin and valproate	**Levels increased:** carbamazepine-epoxide metabolite of carbamazepine, clobazam, clonazepam, lamotrigine, methsuximide, phenobarbital, phenytoin, and valproate

References

Besag F, Patsalos PN. New developments in the treatment of partial-onset epilepsy. *Neuropsychiatr Dis Treat* 2012;**8**:455–64.

Sachdeo R, Kramer LD, Rosenberg A, *et al*. Felbamate monotherapy: controlled trial in patients with partial onset seizures. *Ann Neurol* 1992;**32**(3):386–92.

Shi LL, Dong J, Ni H, *et al*. Felbamate as an add-on therapy for refractory epilepsy. *Cochrane Database Syst Rev* 2011;**1**:CD008295.

Fingolimod

This drug was the first available oral disease-modifying treatment for RRMS. It was introduced in 2010 and has been shown to reduce relapse rates and the development of MRI lesions to a greater extent than IFN-β1a.

Uses

Licensed uses

In the UK

- *Highly active RRMS*: fingolimod is licensed for 'rapidly evolving severe' RRMS and for RRMS with 'high disease activity despite treatment'.
  - *Rapidly evolving severe* RRMS is defined as two or more disabling relapses in 1 year, with at least one gadolinium-enhancing lesion on brain MRI or a significant increase in T2 lesion load.
  - *High disease activity despite treatment* is defined as either having at least one relapse in the previous year on IFN-β or glatiramer acetate and at least nine T2-hyperintense lesions in brain MRI or one gadolinium-enhancing lesion. This includes patients with unchanged/increased relapse rate or ongoing severe relapses, as compared to the previous year.

However, NICE guidelines only support the prescription of fingolimod for the second category, i.e. highly active RRMS despite IFN-β or glatiramer therapy.

In the USA

- *RRMS*: it is licensed for the treatment of any patient with RRMS.

Presentation

- *Trade name*: Gilenya®. Generics are not available.
- *Formulations*: oral capsule: 500mg.

Mechanism of action

Fingolimod is an S1P receptor modulator that induces internalization of the S1P receptor on the surface of lymphocytes and neurons. This disrupts the mechanism by which naïve T cells are drawn from a low concentration of S1P in lymph nodes to a higher concentration of S1P in the circulation. Fingolimod therefore prevents lymphocyte migration to the CNS by sequestration in secondary lymphoid tissues. It may also cross the blood–brain barrier and act on S1P receptors expressed by different types of cells within the CNS. Effector memory T cells are not sequestered and may have increased suppressive functions.

Toxicity and side effects

- *Common—cardiovascular*: bradycardia and hypertension. *Dermatological*: alopecia, eczema, herpes simplex infection, and pruritus. *Endocrine*: hypertriglyceridaemia and weight loss. *Gastrointestinal*: diarrhoea and elevated LFTs. *Haematological*: leucopenia.

Musculoskeletal: back pain. *Neurological*: asthenia, dizziness, headache, migraine, and paraesthesiae. *Ophthalmological*: blurred vision and eye pain. *Psychiatric*: depression. *Respiratory*: bronchitis, cough, dyspnoea, influenza, and sinusitis.

- *Serious—cardiovascular*: AV block. *Haematological*: increased risk of B and T cell lymphoma. *Immunological*: increased risk of all infections. *Neurological*: Several cases of PML have occurred on fingolimod, including in patients not previously on immunosuppressants, PRES. *Ophthalmological*: macular oedema.

Contraindications

- *Absolute*: pre-existing immunodeficiency, hypersensitivity, severe active infection, active chronic infections, severe hepatic impairment (Child–Pugh class C), and active malignancy (excluding basal cell carcinoma).
- *Relative*: severe respiratory disease, recent MI or stroke, risk of QT prolongation or bradycardia, and concurrent use of class Ia or III antiarrhythmics. Caution should be used during initiation in patients with mild or moderate hepatic impairment, but no dose adjustments are required. This drug has not been studied in patients with renal impairment, but no dose adjustments are necessary.

Use in special populations

- *Elderly*: fingolimod should be used with caution in the elderly, in whom the drug has not been studied.
- *Pregnancy*: fingolimod is teratogenic. A negative pregnancy test is required prior to initiation, and active contraception should be used during, and for 2 months following, treatment.
- *Lactation*: it should not be used, while breastfeeding.

Efficacy

The *FREEDOMS* trial demonstrated a 54% reduction in ARR, compared with placebo, significant reduction in risk of disability progression sustained at 3 and 6 months, and 30% reduction in rate of brain volume loss on MRI that persisted for 4 years (*FREEDOMS* extension phase). The *TRANSFORMS* trial showed a relative reduction in ARR of 38–52% with fingolimod, compared to IFN-β1a, and fewer new and enlarging MRI lesions and less brain atrophy.

Dosing and monitoring

Dosing

The drug is administered as an oral dose of 500 micrograms od.

Routine monitoring

A washout period following other immunosuppressant therapy may be required prior to treatment initiation (see individual agents). FBC, LFTs, and ECG should be performed in all patients prior to treatment. Vaccination against VZV should be administered prior to initiation if there is no evidence of immunity, and pregnancy tests should be performed in all women. All patients should be observed for bradycardia for 6h following their first dose. FBC and LFTs should be reviewed at 1, 3, and 6 months, and an ophthalmological examination performed in all patients at 3–4 months. Treatment should be stopped if the lymphocyte count falls below 0.2×10^9/L or if LFTs exceed five times the upper limit of normal.

Pharmacokinetics and interactions

Pharmacokinetics

The oral bioavailability of fingolimod is 93%. Peak plasma concentration occurs at 12–16h. Steady-state concentrations are reached within 2 months. Food intake does not alter absorption. It is phosphorylated to its active form after oral ingestion. Fingolimod and its phosphorylated form are highly protein-bound and extensively distribute to bodily tissues. It is metabolized predominantly by CYP4F2 in the liver. The half-life is 6–9 days. Of an oral dose, 81% is excreted as inactive metabolites by the kidneys, and some is also excreted in faeces. The duration of effect is prolonged, and side effects can persist for 8 weeks after treatment cessation. After this time, alternative immunomodulation can be initiated.

Interactions See Table A.70.

Table A.70 Interactions of fingolimod

Pharmacodynamic interactions
With amiodarone, β-blockers, diltiazem, disopyramide, dronedarone, ketoconazole, and verapamil: there is an increased risk of bradycardia
With vaccinations: immunizations will be less effective during treatment and for up to 6 weeks after treatment

References

Cohen JA, Barkhof F, Comi G, *et al.*; TRANSFORMS Study Group. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010;**362**(5):402–15.

Kappos L, Radue EW, O'Connor P, *et al.*; FREEDOMS Study Group. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010;**362**(5):387–40.

Fludrocortisone

Fludrocortisone was first used in the 1950s for primary and secondary adrenocortical insufficiency in Addison's disease. It can be used in the management of orthostatic hypotension when conservative measures have failed in PD and other disorders associated with an autonomic neuropathy.

Uses

Licensed uses

- Fludrocortisone has no licensed neurological uses.

Off-licence uses

- Orthostatic hypotension associated with autonomic neuropathy, MSA, and PD.

Presentation

- *Trade names*: Florinef®. Generics are available.
- *Formulations*: fludrocortisone is available as 100-microgram tablets.

Mechanism of action

Fludrocortisone is a synthetic mineralocorticoid with minimal glucocorticoid effects. It increases renal sodium reabsorption and expands plasma volume.

Toxicity and side effects

Corticosteroid side effects are uncommon with fludrocortisone at the doses used to treat postural hypotension (see Corticosteroids, pp. 304–8).

- *Common—cardiovascular*: fluid retention, hypertension, and hypokalaemia. *Neurological*: headache when supine.
- *Serious—cardiovascular*: congestive heart failure in susceptible patients, cardiac arrhythmias or ECG changes due to potassium deficiency. *Haematological*: thromboembolism.

Contraindications

- *Absolute*: hypersensitivity to fludrocortisone or its excipients, and untreated systemic infection.
- *Relative*: caution should be used with patients with known electrolyte disturbance or fluid overload. For further contraindications of corticosteroids, see Corticosteroids, pp. 304–8. Fludrocortisone should be used with caution in patients with hepatic or renal impairment, although no dose adjustment is routinely recommended.

Uses in special populations

- *Elderly*: systemic corticosteroid side effects are commoner in the elderly, and closer monitoring is required.
- *Pregnancy*: use in pregnancy has been associated with *in utero* growth retardation and cleft palate deformity. Use only if benefits outweigh risks. Dose alteration is not required. Newborns should be monitored for hypoadrenalism.
- *Lactation*: corticosteroids are found in breast milk. Fludrocortisone should be used with caution in nursing mothers, and the infant monitored for signs of hypoadrenalism.

Efficacy

In PD, the prevalence of orthostatic hypotension may be as high as 60%. However, there is a lack of robust trial evidence for the efficacy of fludrocortisone in PD. Small studies have suggested that it may be safe in this context. Expert consensus suggests that it is an effective treatment option if non-pharmacological therapies have failed.

Dosing and monitoring

Dosing

Start treatment at 50–100 micrograms/day, and increase the dose by 50–100 micrograms in 1-week intervals, as required, to a recommended maximum of 300 micrograms/day.

Routine monitoring

Monitor electrolytes periodically. Potassium supplementation may be required.

Pharmacokinetics and interactions

Pharmacokinetics

Fludrocortisone is rapidly and completely absorbed after oral administration. T_{max} is 4–8h. It is 70–80% bound to plasma proteins. The plasma half-life is ~3.5h. ~80% is excreted in the urine; a small amount is excreted in the faeces.

Interactions See Table A.71.

Table A.71 Interactions of fludrocortisone

Pharmacodynamic interactions
With diuretics: can enhance hypokalaemia

Also see Corticosteroids, pp. 304–8.

Reference

Senard JM, Brefel-Courbon C, Rascol O, Montastruc JL. Orthostatic hypotension in patients with Parkinson's disease: pathophysiology and management. *Drugs Aging* 2001;**18**(7):495–505.

Gabapentin (including gabapentin enacarbil)

Gabapentin was initially marketed as an antiepileptic in the 1990s. It was deliberately designed to mimic the inhibitory neurotransmitter GABA. In fact, the best evidence suggests it probably works via an alternative mechanism. Due to its narrow spectrum of activity and limited efficacy, it is not commonly used in the management of epilepsy but has found use in the treatment of a large number of other neurological disorders, most commonly neuropathic pain.

Gabapentin enacarbil is a new prodrug of gabapentin which has up to double the oral bioavailability of gabapentin. It is not widely available in Europe and is not licensed in the UK. It is predominantly used in the management of RLS, for which it was approved by the FDA in 2011. The majority of the information with regard to gabapentin enacarbil is similar to that of gabapentin, and variations between the two drugs are highlighted below.

Uses

1. *Gabapentin*.

Licensed uses

In the UK/USA

- *Epilepsy*: gabapentin is licensed as a monotherapy for the treatment of focal-onset seizures, with or without secondary generalization, in individuals aged 12 years and older (UK and USA). As an adjunct, it is licensed for the treatment of focal-onset seizures, with or without secondary generalization, in individuals aged 6 years and older in the UK and aged 3 years and older in the USA.
- *Neuropathic pain*: gabapentin is licensed for the treatment of peripheral neuropathic pain in individuals aged 18 years and older. (In the USA, its licence is limited to the treatment of post-herpetic neuralgia.)

Off-licence uses

- Central neuropathic pain, ET, insomnia, PLMS, prophylaxis of migraine, spasticity (in MS and spinal cord injury/disease), SUNCT, and trigeminal neuralgia. Standard-formulation gabapentin has also been used off-licence in the management of RLS.

2. Gabapentin enacarbil.

Licensed uses

In the USA

- *Neuropathic pain*: gabapentin enacarbil is licensed for the treatment of post-herpetic neuralgia in individuals aged 18 years and older.
- *RLS*: gabapentin enacarbil is licensed for the treatment of moderate to severe RLS in individuals aged 12 years and older.

Presentation

1. *Gabapentin*.
   - *Trade names*: Gralise® and Neurontin®. Generics are available.
   - *Formulations*: gabapentin is available as a capsule, an oral solution, and a tablet. Capsule: 100mg, 300mg, and 400mg. Oral solution: 50mg/mL. Tablet: 600mg and 800mg.

2. Gabapentin enacarbil.
   - *Trade names*: Horizant®. Generics are not available.
   - *Formulations*: gabapentin enacarbil is available as extended-release tablets in 300mg and 600mg doses.

Mechanism of action

The exact mechanism of action of gabapentin has not been fully determined. *In vitro* studies have shown it binds to the α2δ subunit of VGCCs. This binding closes presynaptic calcium channels and supresses neuronal activity; this presumably inhibits the activity of nociceptive neurons, as well as pathways involved in the generation of epileptic activity, movement disorders, and spasticity. Gabapentin enacarbil is the prodrug of gabapentin, which is believed to be responsible for the majority of its therapeutic action.

Toxicity and side effects

- *Common—cardiovascular*: hypertension, peripheral oedema, and vasodilatation. *Dermatological*: acne, facial oedema, rash, purpura, and pruritus. *Gastrointestinal*: abdominal pain, bowel disturbances, changes in weight (more commonly weight gain than loss), dry mouth, dyspepsia, gingivitis, nausea, and vomiting can occur. *Haematological*: leucopenia. *Immunological*: fever and flu-like symptoms. *Musculoskeletal*: myalgia and arthralgia. *Neurological*: the commonest side effects are ataxia, dizziness, and fatigue (dose-related and may settle if doses are reduced). Less commonly, amnesia, convulsions, dysarthria, headache, insomnia, movement disorders, paraesthesiae, and speech disorders. *Ophthalmological*: amblyopia and diplopia. *Psychiatric*: anxiety, confusion, depression, labile affect, and hostility. *Respiratory*: bronchitis, cough, dyspnoea, pharyngitis, and rhinitis.
- *Serious—dermatological*: angio-oedema and Stevens–Johnson syndrome can occur. *Gastrointestinal*: rarely, hepatitis and pancreatitis have been reported. *Immunological*: rarely, patients can develop a hypersensitivity syndrome. *Psychiatric*: suicidal ideation has been reported. *Renal*: acute renal failure is a rarely reported adverse event.

Contraindications

- *Absolute*: hypersensitivity to gabapentin, pregabalin, or any excipient.
  1. *Gabapentin*.
- *Relative*: gabapentin may exacerbate generalized seizures. It should be used with caution in individuals with a history of psychotic illness. Gabapentin is primarily renally excreted, and hence dosing needs to be adjusted, depending on the eGFR: If the eGFR is 50–80mL/min/1.73m^2, the dose should be reduced to a maximum of 1.8g daily; if the eGFR is 30–50mL/min/1.73m^2, the dose should be reduced to a maximum of 900mg daily; if the eGFR is 15–30mL/min/1.73m^2, the dose should be reduced to 300mg on alternate days up to a maximum of 600mg daily; if the eGFR <15mL/min/1.73m^2, the dose should be reduced in proportion to the eGFR. No dose adjustments are required in hepatic impairment.

  2. Gabapentin enacarbil.

- *Relative*: no dose adjustment is required in hepatic impairment. Dose adjustment is not necessary for patients with CrCl ≥60mL/min. For patients with CrCl 30–59mL/min, the recommended initial dose is 300mg/day and may be increased to 600mg/day, as needed. When CrCl is 15–29mL/min, the recommended dose is 300mg daily, and 300mg every other day when CrCl is <15mL/min.

Uses in special populations

- *Elderly*: the elderly are more susceptible to side effects, e.g. falls, tiredness, and weakness. There is also an age-related decline in renal function, and hence lower doses should be used.
- *Pregnancy*: gabapentin and gabapentin enacarbil have not been adequately studied in pregnancy. Animal studies have demonstrated teratogenic effects; however, there are no studies in humans. Use in pregnancy involves weighing up the potential benefits and side effects. The pharmacokinetics of gabapentin do not change during pregnancy.
- *Lactation*: breastfed infants are exposed to gabapentin in maternal milk. An infant can expect to have gabapentin levels of 4–12% that of the mother. If used, infants should be monitored for side effects, and an alternative feeding regimen used if these are identified.

Efficacy

- *Epilepsy*: there is little good-quality evidence supporting the use of gabapentin in epilepsy. Expert consensus suggests that gabapentin is more effective than placebo as monotherapy in the treatment of focal-onset epilepsy. The SANAD study, a large unblinded trial conducted in the UK, found gabapentin to be significantly less effective than carbamazepine or lamotrigine for the same indication.
- *ET*: a double-blind, multiple-dose, placebo-controlled cross-over trial ($n = 25$) of gabapentin found significant improvements in global assessments ($p < 0.05$), observed tremor scores ($p < 0.005$), water pouring scores ($p < 0.05$), and activities of daily living scores ($p < 0.005$). Tremor amplitude scores did not improve in this study. However, amplitudes measured by accelerometry in another RCT ($n = 16$) found gabapentin (1200mg/day) reduced tremor amplitude at day 15 by 77%.
- *Headache*: a Cochrane review of gabapentin in the prophylaxis of episodic migraine found that, in the pooled analysis, there was no difference between gabapentin and placebo in reducing the frequency of headache at doses ranging from 1200mg to 2000mg. There was no evidence of increasing efficacy with higher doses. When analysed separately, two trials showed a modest benefit of active treatment over placebo. Gabapentin is currently a second-line agent in the UK for migraine prophylaxis. It has also been shown in published case series to be effective in the prophylaxis of SUNCT where it is used as a third-line agent, after lamotrigine and topiramate.
- *Neuropathic pain*: a recent systematic review identified 29 studies involving 3571 participants with various neuropathic pain syndromes treated with gabapentin. Gabapentin showed statistical efficacy (50% pain reduction), compared to placebo, in treating painful diabetic neuropathy (829 participants), with an NNT of 5.8 (95% CI 4.3–9.0),

and in treating post-herpetic neuralgia (892 participants), with an NNT of 7.5 (95% CI 5.2–14) for 50% pain reduction. A small study also showed a small benefit from gabapentin treatment in pain relief in patients with fibromyalgia. Two recent systematic reviews have shown that gabapentin is effective at producing good relief from neuropathic pain post-spinal cord injury and in phantom limb pain.

- *RLS*.
  1. Gabapentin: a double-blind, placebo-controlled, cross-over study (n = 24) found gabapentin (mean effective dose 1855mg/day) treatment after 6 weeks reduced the mean RLS rating scale score by 10.5 vs. 2.1 with placebo (p <0.001). Gabapentin also improved sleep quality, reduced periodic leg movements of sleep, and clinical global impression of change.
  2. Gabapentin enacarbil: a 12-week multicentre RCT (n = 222) of gabapentin enacarbil found an average difference in International Restless Legs Scale (IRLS) score of −4.0 (95% CI −6.2 to −1.9; p = 0.0003). 76% of patients treated were responders, compared to 39% with placebo (p <0.0001). Long-term efficacy and safety were shown in a 52-week extension study (n = 573) in patients with moderate to severe RLS. Adverse events were reported in 80% of subjects; however, they led to study withdrawal in only 10%. At the end of the study period, subjects had an average difference in IRLS of −15.2, and 85% were Clinical Global Impression–Improvement scale responders.
- *Spasticity*: gabapentin was first trialled as a spasticity therapy in the late 1990s. A handful of small, randomized, placebo-controlled trials and observational studies found it to be effective in treating spasticity secondary to MS or spinal cord injury by various measures (including modest improvements in Ashworth score). In the context of spasticity, there are no systematic reviews, meta-analyses, or comparative studies of efficacy or tolerability available.

Dosing and monitoring

Dosing

Dosing is similar for all indications. Start treatment at 300mg/day on day 1, 300mg bd on day 2, and 300mg tds on day 3. Then gabapentin is increased by 300mg/day in 2–3 divided doses every 3 days. Alternatively, in young patients with normal renal function where rapid disease control is required, 300mg tds can be used from day 1 and uptitrated, as previously suggested. The normal maintenance dose is between 0.9g and 2.4g daily in three divided doses. The maximum dose is 3.6g/day in three divided doses, although side effects are likely to predominate at daily doses higher than 2.4g.

Routine monitoring

Liver and renal function tests should be performed before starting the medication and yearly thereafter while therapy is continued. Diabetic patients will require close monitoring of blood glucose levels. Weight and BMI will also need to be regularly reviewed.

Therapeutic drug monitoring

Optimum seizure control, when used in monotherapy, occurs at plasma concentrations of 2–20mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

- *Gabapentin enacarbil*: in the fed state, it has a bioavailability of 75% (45–65% fasting). It undergoes first-pass hydrolysis, predominantly by enterocytes, to gabapentin. T_{max} of gabapentin is reached in 5–7h, with steady state reached in 2 days (blood levels of gabapentin enacarbil are very low and thought to be insignificant). The rest of the pharmacokinetic profile is as for gabapentin.
- *Gabapentin*: ~60% of a 300mg capsule reaches the bloodstream. The bioavailability reduces markedly at higher doses. Food co-ingestion will further reduce the extent of absorption by 25% and delays absorption by 2–3h. T_{max} occurs at ~2h; this is faster at larger doses. Steady state is reached in 1–2 days. 0% is protein-bound. The half-life is 5–9h. Pharmacokinetics are non-linear, due to saturable absorption. Elimination is directly proportional to the eGFR, as there is 100% renal excretion and no hepatic metabolism.

Interactions See Table A.72.

Table A.72 Interactions of gabapentin

Medications which alter gabapentin plasma levels	Medications whose plasma levels are altered by gabapentin
Levels decreased: antacids	**Levels decreased:** pregabalin
Levels increased: cimetidine, naproxen, hydrocodone, and morphine	**Levels increased:** felbamate

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Glatiramer acetate

This drug, also known as copolymer 1, is a mixture of polypeptides that was first shown to reduce relapse rates in MS in 1995. It remains a first-line treatment option in RRMS. It is an established drug with many years of clinical experience and a good safety profile. Its role has diminished recently with the advent of newer agents, which can be administered orally and are probably more effective at reducing relapses e.g. dimethyl fumarate, but come with the compromise of a worse safety profile.

Uses

Licensed uses

In the UK/USA

- *RRMS*: glatiramer acetate is licensed for RRMS. Licensing in the UK requires there to be at least two relapses over the preceding 2 years.
- *Clinically isolated syndrome*: glatiramer acetate is also licensed for patients with a single demyelinating event with an active inflammatory process. In the USA, this requires evidence of MRI features consistent with MS, and, in the UK, this requires that patients be deemed at high risk of developing clinically definite MS.

Off-licence uses

- None.

Presentation

- *Trade name*: Copaxone®. Generics are not available.
- *Formulation*: solution for SC injection in pre-filled syringes: 20 and 40mg.

Mechanism of action

Glatiramer acetate is a salt mixture of polypeptides consisting of random combinations of four *L*-amino acids—alanine, glutamate, lysine, and tyrosine are present in specific molar fractions within this mixture. The mechanism of action is complex and not entirely understood. The polypeptide mixture is antigenically similar to myelin basic protein and demonstrates strong binding to MHC molecules. It prevents the presentation of myelin antigens to T cells and may also induce T helper 2 (Th2) suppressor cells that migrate to sites of CNS inflammation.

Toxicity and side effects

- *Common—cardiovascular*: palpitations and tachycardia. *Dermatological*: benign skin cancer, ecchymosis, flushing, injection site atrophy and reactions, pruritus, and urticaria. *Gastrointestinal*: anorexia, constipation, dyspepsia, dysphagia, gastroenteritis, vomiting, and weight gain. *Immunological*: fever, lymphadenopathy, and rigors. *Musculoskeletal*: arthralgia, and back and neck pain. *Neurological*: dysgeusia, headache, hypertonia, and tremor. *Ophthalmological*: cataracts and diplopia. *Psychiatric*: anxiety and depression. *Respiratory*: bronchitis, dyspnoea, influenza, otitis media, and rhinitis.
- *Serious—genitourinary*: urinary retention. *Haematological*: leucopenia and thrombocytopenia. *Immunological*: hypersensitivity and an increased risk of infections. *Ophthalmological*: optic atrophy. *Psychiatric*: psychosis.

Contraindications

- *Absolute*: hypersensitivity to glatiramer acetate (or mannitol) and pregnancy.
- *Relative*: the effect of the drug on patients with hepatic and renal impairment has not been studied, and caution with careful monitoring is advised.

Use in special populations

- *Elderly*: glatiramer acetate has not been studied in the elderly and should be used with caution.
- *Pregnancy*: it can be continued during attempts to conceive but should be stopped when pregnancy is confirmed. The effects on pregnancy and fetal development are not clear.
- *Lactation*: it should not be used while breastfeeding.

Efficacy

Glatiramer acetate reduces the ARR by ~30% in pivotal and subsequent trials. Overall efficacy is considered broadly equivalent to IFN-β (BEYOND trial).

Dosing and monitoring

Dosing

Glatiramer acetate is administered as either an OD 20mg or 3 times weekly (at least 48 hours apart) 40mg SC injection.

Routine monitoring

No specific monitoring is required. Patients should be informed that flushing, dyspnoea, palpitations, chest pain, and tachycardia may occur within minutes of initial injections and are typically short-lived without any complications. No data exist to support the need for a washout period before switching to an alternative immunomodulatory agent. It is generally stopped for 4–6 weeks prior to the initiation of natalizumab, but no washout period is needed when switching to IFN-β or fingolimod.

Pharmacokinetics and interactions

Pharmacokinetics

There is limited information on the absorption, distribution, or excretion of this drug, because there are no accurate *in vivo* assays for measuring glatiramer acetate or its breakdown products. *In vitro* studies suggest that metabolism occurs at the site of injection.

Interactions None.

References

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Glyceryl trinitrate

GTN is an organic nitrate, which was first synthesized in 1846. It is widely used as a buccal spray in the management of angina pectoris and has been marketed in the UK since the 1930s. It is used off-licence as an infusion for the management of severe hypertension in acute stroke. Trials are ongoing as to whether its use in this setting has a beneficial effect on functional outcomes.

Uses

Licensed uses

In the UK/USA

GTN has no licensed neurological uses.

Off-licence uses

GTN infusion can be used in acute stroke if there is evidence of malignant hypertension or to lower the BP to <185/110mmHg in patients with ischaemic stroke who are potential candidates for alteplase. The effectiveness of a GTN patch to lower the BP in lesser degrees of hypertension is currently under assessment in clinical trials.

Presentation

- *Trade names*: Nitrocine® and Nitronal®. Generics are available.
- *Formulations*: GTN is available in both oral and parenteral forms; in the context of acute ischaemic stroke, only an IV infusion is routinely used. This is available at concentrations of 1mg/mL and 5mg/mL, in 5mL and 10mL vials for further dilution.

Mechanism of action

GTN is an organic nitrate that releases NO following enzymatic denitration. NO has several important functions, including relaxation of vascular smooth muscle cells via the activation of soluble guanylate cyclase and the formation of cyclic guanosine monophosphate (GMP). NO also inhibits platelet aggregation and leucocyte–endothelial interactions. At high doses, nitrates produce arterial vasodilatation, reducing systemic vascular resistances, and hence rapid BP reduction.

Toxicity and side effects

- *Common—cardiovascular*: palpitations, paradoxical bradycardia, postural hypotension, syncope, and tachycardia. *Dermatological*: diaphoresis, flushing, and rash. *Gastrointestinal*: abdominal pain, heartburn, nausea, and vomiting. *Haematological*: anaemia, thrombocytopenia. *Immunological*: allergic reaction. *Neurological*: dizziness, headache, and muscle twitching.
- *Serious—cardiovascular*: crescendo angina, severe hypotension, and cardiovascular collapse. *Immunological*: anaphylaxis. *Haematological*: methaemoglobinaemia.

Contraindications

- *Absolute*: hypersensitivity to nitrates, hypotensive conditions (systolic BP <100) and hypovolaemia, hypertrophic cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis, toxic pulmonary oedema, raised ICP (not due to malignant hypertension), marked anaemia.
- *Relative*: use with caution in severe renal impairment and/or severe hepatic impairment, hypothermia, and hypothyroidism.

Uses in special populations

- *Elderly*: no additional dose adjustments are required—rate of infusion needs to be titrated to individual response.
- *Pregnancy*: the safety of nitrates in pregnancy has not been established. They should only be given if benefits outweigh risks.
- *Lactation*: the safety of nitrates in nursing mothers has not been established. They should only be given if benefits outweigh risks.

Efficacy

A Cochrane review has analysed evidence from 12 small trials, which set out to investigate whether BP modification improved outcomes in either acute ischaemic or haemorrhagic stroke. There was insufficient evidence to demonstrate any difference in functional neurological outcomes. Several larger studies are currently ongoing and will hopefully provide results to guide management in this currently controversial area. In addition, the Rapid Intervention with Glyceryl Trinitrate in Hypertensive stroke trial has assessed the safety and efficacy of transdermal GTN in the management of stroke with hypertension. The implications of the patch on functional outcomes in stroke is currently under active investigation.

Dosing and monitoring

Dosing

There are no specific dosing instructions provided by manufacturers for this indication. Start treatment at 10–25 micrograms/min, depending on local hospital protocols; this can be increased in increments of 5–10 micrograms, until a desired BP is reached or GTN is no longer tolerated (usually due to headache). The maximum rate is 400 micrograms/min.

Monitoring Regular monitoring of BP and heart rate is required.

Pharmacokinetics and interactions

Pharmacokinetics

GTN is metabolized hepatically by a reductase to dinitrate and mononitrate. It then undergoes glucuronidation. Spontaneous hydrolysis in the plasma also occurs. The half-life is usually 1–3min. The metabolites are predominantly eliminated by the renal tract.

Interactions See Table A.73.

Table A.73 Drug interactions of GTN

Pharmacodynamic interactions
With other antihypertensives, e.g. ACE inhibitors: enhanced hypotensive effect
With heparin: reduced anticoagulant effect of heparin
With corticosteroids and NSAIDs: antagonism of hypotensive effect

References

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Haem-like therapies

Hemin therapies, most commonly in the form of lyophilized hematin (Panhematin®) and heme arginate (Normosang®), are used in the management of acute attacks of hepatic porphyrias. Heme arginate was first marketed in the UK in 1999. They are more effective than carbohydrate loading and should be started as soon as possible in the management of an acute attack, as their effects may be delayed if started late.

Uses

Licensed uses

In the UK

- *Inborn errors of metabolism*: heme arginate (Normosang®) is licensed for the treatment of acute porphyrias (acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria) in individuals of all ages.

In the USA

- *Inborn errors of metabolism*: lyophilized hematin (Panhematin®) is licensed for the treatment of recurrent attacks of acute intermittent porphyria temporally related to the menstrual cycle in susceptible women in individuals aged 16 years and older.

Off-licence uses

- As prophylactic treatment in the management of acute porphyrias. Panhematin® is also used off-licence in the management of other acute porphyrias.

Presentation

- *Trade names*: Normosang® and Panhematin®. Generics are not available.
- *Formulations*: Normosang® is available as a concentrate for IV infusion, in 10mL ampoules (25mg/mL). Panhematin® is available as a powder for IV infusion after reconstitution in vials containing 313mg of hemin.

Mechanism of action

In the acute prophyrias, there is reduced activity or deficiency of one of a number of enzymes involved in haem synthesis, resulting in a deficiency in haem and a build-up of toxic precursors. IV haem-like compounds hematin and heme arginate are believed to act by replenishing the depleted haem pool and thereby initiating negative feedback processes, which suppress hepatic aminolevulinate synthase activity, an enzyme important in the generation of porphyrins and other toxic haem precursors.

Toxicity and side effects

- *Serious—dermatological*: rarely anaphylaxis and hypersensitivity reactions. *Haematological*: thrombophlebitis and venous thrombosis are common and are probably the result of degradation products which form rapidly *in vitro* when lyophilized hemin is reconstituted with sterile water.

Contraindications

- *Absolute*: hypersensitivity to the drug to be used.
- *Relative*: studies have not been performed in patients with hepatic or renal impairment; hence these drugs should only be used with caution in these patient groups.

Uses in special populations

- *Elderly*: there are no data on the safety and efficacy of heme arginate in patients above 65 years of age; use with caution.
- *Pregnancy*: limited data are available, and the manufacturer advises to avoid. However, experience indicates that heme arginate can be administered safely during pregnancy. Use if the benefits outweigh the risks of no treatment.
- *Lactation*: no information is available as to whether haem-like drugs are excreted in breast milk; the manufacturer advises to avoid use in nursing mothers.

Efficacy

There are many uncontrolled clinical studies suggesting a favourable clinical response to hemin treatment in the management of acute porphyrias; however, only a few placebo-controlled trials have been conducted. A double-blind, placebo-controlled trial of hemin therapy in 12 patients with acute porphyria showed striking decreases in urinary porphobilinogen excretion and trends in clinical benefit (less pain, decreased need for pain medication, and shortened hospital stays) in patients treated with hemin.

A larger, but uncontrolled, study of 22 patients with acute attacks of porphyria who received heme arginate treatment within 24h of admission showed that all patients responded to treatment, as demonstrated biochemically by a decrease in mean urinary excretion of porphobilinogen and ALA levels and clinically by the fact that hospitalization was <7 days in 90% of cases. A growing body of evidence has led to the current consensus that early initiation of IV hemin treatment in acute attacks of porphyria is associated with improved outcomes.

Dosing and monitoring

Dosing

Start treatment as soon as acute porphyria is recognized.

- Normosang®: administer 3mg/kg (maximum 250mg daily) in 100mL of 0.9% saline over 30min IV od for 4 days. Clinical improvement is often rapid and usually evident within 1–2 days.
- Panhematin®: administer 1–4mg/kg/day of hematin—select the dose, depending on the severity of the attack; in very severe cases, a further dose can be given after 12h (maximum 6mg/kg/day). The powder is reconstituted with 43mL of sterile water; hence 1mg of hematin is equivalent to 0.14mL of reconstituted Panhematin®. The dose should be administered over 10–15min by IV infusion, and given for 3–14 days, depending on clinical response.

Routine monitoring

During treatment with haem-like therapies, patients should be monitored closely for complications of acute porphyria, hypersensitivity reactions, and thrombophlebitis. Serial urinary levels of ALA, porphobilinogen, and coproporphyrin may also aid recognition of biochemical response to treatment.

Pharmacokinetics and interactions

Pharmacokinetics

Normosang®: Limited data are available from pharmacokinetic studies; in healthy individuals and patients with porphyria, the elimination half-life of heme arginate ranges from 9h to 12.5h. After repeated infusions, the elimination half-life increases (18h after four infusions). The pharmacokinetics of Panhematin® have not been defined.

Interactions See Table A.74.

Table A.74 Interactions of haem-like therapies

Medications whose plasma levels are altered by Normosang®
Levels decreased: barbiturates, corticosteroids, and the oral contraceptive pill
No interactions have been reported with Panhematin®.

References

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Intravenous immunoglobulin

IVIg is the pooled, highly purified IgG antibody from the serum of over a thousand human donors. It was first used in the 1950s to treat immunodeficiency syndromes. It is currently widely used to treat a variety of autoimmune conditions.

Uses

IVIg is used as an acute, first-line treatment in a wide range of acute autoimmune conditions, and as maintenance therapy in chronic disease poorly responsive to alternative therapies. Licensing laws vary considerably between countries and formulations. A summary (non-exhaustive) of its uses are given below:

- autoimmune limbic encephalitis;
- CANOMAD (first-line, acute);
- CIDP (first-line, acute or chronic);
- Guillain–Barré syndrome (first-line, acute);
- LEMS (refractory cases);
- MMN with conduction block (first-line);
- MG (acute or chronic);
- Neurolupus;
- NMO (second-line);
- PM (refractory cases);
- DM (refractory cases);
- Sjögren's syndrome;
- Stiff person syndrome (refractory cases);
- TM (refractory cases).

In the UK, these indications are prioritized by a colour-coding scheme (red, blue, or grey in descending order), based on availability of alternative treatments and the strength of clinical evidence.

Presentation

- *Trade name*: Aragam®, Flebogamma®, Gammagard S/D®, Gammaked®, Gammaplex®, Gamunex®, Intratect®, Kiovig®, Octagam®, Privigen®, and Vigam®. Generics are not available.
- *Formulation*: IVIg is available as an infusion of 5% protein (Aragam®, Flebogamma®, Gammagard S/D®, Gammaplex®, Intratect® Octagam®, and Vigam®), or 10% protein (Gamunex®, Kiovig®, and Privigen®). 5% protein infusion: 0.5g, 1g, 2g, 2.5g, 5g, 10g, and 20g. 10% protein infusion: 1g, 5g, 10g, 20g, and 30g.

Mechanism of action

The mechanism of action of IVIg remains unclear after many decades of use and experience from both animal and human studies. Its action is paradoxical in that many of the diseases treated with IVIg themselves owe their pathology to the IgG molecule. Several mechanisms have been proposed: $F(ab')_2$-dependent effects (involving the fragment antigen-binding region of the molecule) include the blockade of cell–cell interactions, as IVIg binds cellular surface receptors; neutralization of cytokines and autoantibodies; antibody-dependent cytotoxicity which kills target cells;

and scavenging of anaphylatoxins C3a and C5a. Fc-dependent mechanisms (involving the fragment crystallizable region of the IgG molecule) include expansion of regulatory T cell populations, modulation of dendritic cells, and the blockade of immune complex binding, thereby blocking activating receptors on target cells.

Toxicity and side effects

- *Common—cardiovascular*: hypertension and palpitations. *Dermatological*: injection site reaction, rash. *Gastrointestinal*: abdominal pain, diarrhoea, nausea, and vomiting. *Immunological*: fever, flushing, malaise, rigors. More likely to be severe in patients with pre-existing, chronic, or inadequately treated infections. *Musculoskeletal*: arthralgia and myalgia. *Neurological*: headache. *Renal*: hyponatraemia.
- *Serious—cardiovascular*: hypertension, hypotension, and MI. *Dermatological*: erythema multiforme. *Genitourinary*: acute kidney injury. *Haematological*: haemolytic anaemia. *Immunological*: anaphylaxis and hypersensitivity (especially in IgA-deficient patients). *Infectious*: there is a theoretical risk of seroconversion for blood-borne viruses, i.e. hepatitis and HIV. *Neurological*: aseptic meningitis syndrome and stroke. *Respiratory*: VTE.

Contraindications

- *Absolute*: fructose intolerance, hypersensitivity, and IgA deficiency.
- *Relative*: the risk of acute kidney injury is increased with preparations with added sucrose, underlying renal disease, diabetes mellitus, advanced age, volume depletion, sepsis, paraproteinaemia, and co-prescription of nephrotoxic drugs. Caution advised in patients with pre-existing renal impairment. No dose adjustment is required in hepatic impairment.

Uses in special populations

- *Elderly*: a lower concentration and/or slower rate of IVIg infusion should be used in elderly patients, due to the increased risk of renal impairment.
- *Pregnancy*: IVIg crosses the placenta. Experience suggests that there are no harmful effects on the course of pregnancy or the fetus, but caution is advised.
- *Lactation*: IVIg is excreted into breast milk, and caution during breastfeeding is recommended.

Efficacy

IVIg is used to treat a large number of autoimmune disorders. For a discussion with regard to the evidence base for use in these indications, please see the individual conditions.

Dosing and monitoring

Dosing

Regimens vary according to indications and preparations, but typically IVIg is prescribed at 0.4g/kg/day over 5 days (i.e. 2g/kg in total). An initial rate of infusion of 0.01–0.02mL/kg/min is typical for 5% IVIg for the first 30min. This can be increased gradually, as tolerated, to a maximum

of 0.1mL/kg/min. This is based on dosing regimens used in initial experience of the drug, but optimum dosing regimens and durations of therapy are yet to be established. Paracetamol, antihistamines, and glucocorticoids are often administered as pre-medications for their antipyretic and anti-inflammatory properties for IVIg-naïve patients or on changing brands. Good hydration should be ensured prior to commencing IVIg infusion to avoid thrombotic and nephrotoxic complications of therapy.

Monitoring

Serum IgA levels and renal function should be checked prior to treatment initiation. Blood-borne viral serology may be taken prior to the first treatment, as IVIg is a blood product and there is a rare potential risk of viral seroconversion following infusion. Patients should be monitored closely during the first dose for infusion reactions. These are more likely during the first dose, with high infusion rates and with long delays since the last dose. If side effects occur, the infusion should be stopped, and the patient appropriately treated. Depending on the nature of the side effect, the infusion can be recommenced at a lower rate and increased as tolerated. Renal function and FBC should be monitored following a course of treatment.

Pharmacokinetics and interactions

Pharmacokinetics

The immunoglobulin is distributed rapidly within the plasma and extracellular fluid, reaching steady state at 3–5 days. Immunoglobulins and their complexes are mostly broken down by the reticuloendothelial system. The half-life varies between patients and preparations. The mean half-life is 21.7 days, following the first dose of a commonly used preparation.

Interactions

IVIg may impair the immune response to live virus vaccines. These should only be given 3 weeks before, or 3 months after, IVIg. There are no other specific interactions.

References

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Schwab I, Nimmerjahn F. Intravenous immunoglobulin therapy: how does IgG modulate the immune system? *Nat Rev Immunol* 2013;**13**(3):176–89.

Labetalol

Labetalol is an antagonist at both β-adrenergic and α1-adrenergic receptors. It is used in the treatment of hypertension associated with a variety of conditions and was first marketed in the UK during the 1980s.

Uses

Licensed uses

In the UK/USA

There are no licensed neurological uses.

Off-licence uses

Labetalol infusion can be used in acute stroke if there is evidence of malignant hypertension or to lower the BP to <185/110mmHg in patients with ischaemic stroke who are potential candidates for alteplase.

Presentation

- *Trade name*: Trandate®. Generics are available.
- *Formulations*: labetalol is available in both PO and parenteral forms. In the context of acute ischaemic stroke, only the IV route is routinely used. This is available as a solution at a concentration of 5mg/mL in 4mL, 20mL, and 40mL vials.

Mechanism of action

Labetalol acts by blocking α- and β-adrenergic receptors, resulting in decreased peripheral vascular resistance, while preventing the reflex tachycardia, thereby maintaining a low BP.

Toxicity and side effects

- *Common—cardiovascular*: bradycardia, postural hypotension, and syncope (avoid the upright position during, and for 3h after, IV administration). *Dermatological*: flushing and rash. *Gastrointestinal*: epigastric pain. *Immunological*: allergic reaction. *Neurological*: dizziness and headache.
- *Serious—gastrointestinal*: hepatocellular damage.

Contraindications

- *Absolute*: hypersensitivity to labetalol, uncontrolled heart failure, Prinzmetal's angina, marked bradycardia, hypotension, sick sinus syndrome, second- or third-degree AV block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease. Avoid in those with hepatic impairment, as severe hepatocellular injury has been reported.
- *Relative*: first-degree AV block, asthma, or other obstructive airway disease. No dose adjustments are routinely recommended in hepatic or renal impairment. However, labetalol should be used in caution with hepatic impairment, as hepatocellular injury can occur, and labetalol is predominantly eliminated in the urine; hence dose adjustment may be required in renal impairment.

Uses in special populations

- *Elderly*: the elderly are more prone to pre-existing cardiovascular disease and are more at risk of postural hypotension and falls. Labetalol should be used with caution in this group.
- *Pregnancy*: no teratogenic effects have been identified in animal studies; however, labetalol crosses the placental barrier and will increase the risk of fetal bradycardia, distress, respiratory depression, and both cardiac and respiratory complications when used late in labour for the neonate post-natally. It should only be given if the benefits outweigh the risks.
- *Lactation*: labetalol is present in breast milk, and hence manufacturers recommend that it should be avoided in nursing mothers.

Efficacy

The CHHIPS trial was a double-blind RCT of 179 patients that looked at the acute treatment with labetalol or lisinopril for those with systolic BP >160mmHg in the context of acute ischaemic and haemorrhagic stroke. Within 36h of symptom onset, patients were either assigned to oral labetalol, lisinopril, or placebo, or to IV labetalol, sublingual lisinopril, or placebo if suffering from dysphagia. The primary outcome assessed was mortality or dependency at 14 days post-symptom onset; this occurred in 61% of patients who were actively managed, and 59% of patients treated with placebo (RR 1.03, 95% CI 0.80–1.33; $p = 0.82$). No acute neurological deterioration was noted in the actively treated group, despite the significantly higher reduction in systolic BP. Importantly, at 3 months post-stroke, the rates of mortality were halved in those who were actively treated (HR 0.40, 95% CI 0.2–1.0; $p = 0.05$). Early lowering of the BP with lisinopril and labetalol after acute stroke seems to be a promising approach to reduce mortality and potential disability.

Dosing and monitoring

Dosing

There are no specific dosing instructions provided by manufacturers for this indication. Treatment can be by repeated IV boluses or IV infusion. IV bolus: give 10–20mg over 10min (consider higher doses if systolic BP >230mmHg or diastolic BP >120mmHg); this can be repeated or doubled every 10min up to a maximum dose of 150–200mg. An IV infusion can be used initially or after repeat boluses. Start the infusion at a rate of 2mg/min, and titrate up to 8mg/min, as required.

Monitoring

Patients should have an ECG performed at baseline to look for any form of heart block. They should then be attached to a cardiac monitor to allow frequent monitoring of BP and heart rate.

Pharmacokinetics and interactions

Pharmacokinetics

Labetalol binds to plasma proteins (90%) and is extensively metabolized in the liver to produce inactive glucuronide metabolites, excreted in the urine (50%) and bile. The plasma half-life is ~4h.

Interactions See Table A.75.

Table A.75 Interactions of labetalol

Medications which alter labetalol plasma levels	Medications whose plasma levels are altered by labetalol	Pharmacodynamic interactions
Levels increased: cimetidine	Levels increased: imipramine	**With other hypotensive agents, e.g. ACE inhibitors:** enhanced hypotensive effect **With antiarrhythmics/calcium channel blockers:** increased myocardial depression/risk of bradycardia/AV block **With hypoglycaemic agents:** beta-blockers may enhance hypoglycaemic effects of insulin **With clonidine:** risk of withdrawal hypertension **With crizotinib, fingolimod, and mefloquine:** increased risk of bradycardia **With ergotamine and methysergide:** increased risk of peripheral vasoconstriction **With heparin:** reduced anticoagulant effect **With corticosteroids and NSAIDs:** reduced hypotensive effect

Reference

Potter JF, Robinson TG, Ford GA, *et al*. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. *Lancet Neurol* 2009;**8**(1):48–56.

Lacosamide

Lacosamide was first marketed in the UK as an AED in 2008. Its main advantage is its paucity of pharmacokinetic interactions, and its main disadvantage is a high incidence of gastrointestinal side effects.

Uses

Licensed uses

In the UK/USA

- *Epilepsy*: lacosamide is licensed for treatment as an adjunct of focal-onset seizures in individuals aged 16 years and older in the UK, and aged 17 years and older in the USA.

Off-licence uses

- Non-convulsive status epilepticus.

Presentation

- *Trade names*: Vimpat®. Generics are not available.
- *Formulations*: lacosamide is available as a film-coated tablet, a solution for IV infusion, and a syrup. Film-coated tablet: 50mg, 100mg, 150mg, and 200mg. Solution for infusion: 10mg/mL in 20mL vials. Syrup: 10mg/mL.

Mechanism of action

The precise mechanism of action of lacosamide is poorly understood. *In vitro* studies have shown that the compound selectively enhances slow inactivation of voltage-gated sodium channels, thereby stabilizing neuronal membranes.

Toxicity and side effects

- *Common—dermatological*: pruritus and rash can occur. *Gastrointestinal*: constipation, flatulence, nausea, and vomiting. *Neurological*: dizziness and headache are very common. Fatigue, impaired concentration and memory, insomnia, tremor, and nystagmus are common. *Ophthalmological*: blurred and double vision. *Psychiatric*: confusion and depression.
- *Serious—cardiovascular*: prolongation of the PR interval, which can lead to arrhythmia, bradycardia, and heart block. *Dermatological*: rarely angio-oedema. *Immunological*: rarely a multiorgan hypersensitivity reaction can occur. *Psychiatric*: psychosis and suicidal ideation have been reported.

Contraindications

- *Absolute*: hypersensitivity to lacosamide or its excipients, and second-/third-degree heart block.
- *Relative*—severe cardiac disease, conduction abnormalities, elderly, and co-administration with drugs that can prolong the PR interval. It is recommended to use lacosamide with caution in severe hepatic impairment, although there is a lack of clinical data in this population. A maximum of 250mg/day is recommended in late-stage renal failure with an eGFR <30mL/min/1.73m^2.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function and benefit from lower dosing regimens.
- *Pregnancy*: lacosamide has not been adequately studied in pregnancy. Animal studies have demonstrated teratogenic effects; however, there are no studies in humans. Use in pregnancy involves weighing up the potential benefits and side effects. It is unknown if the pharmacokinetics of lacosamide change during pregnancy.
- *Lactation*: lacosamide concentration in breast milk has not been studied. If lacosamide is taken during breastfeeding, infants should be monitored for side effects, and an alternative feeding regimen used if these are identified.

Efficacy

The efficacy of lacosamide has mainly been explored in the context of refractory epilepsy. A recent multicentre, double-blind, placebo-controlled trial of patients with focal-onset epilepsy already on two or more AEDs showed that the median percentage reduction in seizure frequency was 35% and 36%, respectively, for 200mg/day and 400mg/day dosing protocols, compared to 20% for placebo. No added benefit has been subsequently shown at higher dosing levels.

Dosing and monitoring

Dosing

For the treatment of epilepsy, start treatment at 50mg bd. This can be increased by 50mg bd in weekly intervals to a recommended maximum dosage of 200mg bd. Enteral and IV formulations are bioequivalent.

Routine monitoring Liver and renal function testing should be performed prior to commencing therapy and then yearly while treatment is ongoing. A baseline ECG is recommended, particularly in the elderly, to rule out heart block.

Therapeutic drug monitoring Optimum seizure control when used in monotherapy occurs at plasma concentrations of 10–20mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is 100%. This is unaffected by food co-ingestion. T_{max} is at 1–2h post-dose. Steady-state plasma levels are reached at 2–3 days. The pharmacokinetics are linear, and <15% of the compound is protein-bound. The elimination half-life is 13h. Sixty per cent of the drug is metabolized by the liver into inactive metabolites. Forty per cent is excreted unchanged by the kidneys, with the majority of the hepatically metabolized product. In total, over 95% of the medication is excreted by the renal system.

Interactions See Table A.76.

Table A.76 Interactions of lacosamide

Medications which alter lacosamide plasma levels	Medications whose plasma levels are altered by lacosamide
Levels decreased: phenobarbital and phenytoin	**Levels decreased:** oxcarbazepine (metabolite)

References

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Halász P, Kalviainen R, Mazurkiewicz-Beldzinska M, *et al*.; the SP755 Study Group. Adjunctive lacosamide for partial-onset seizures: efficacy and safety results from a randomized controlled trial. *Epilepsia* 2009;**50**(3):443–53.

Lamotrigine

Lamotrigine was first marketed in the UK as an AED in 1991. It is a useful broad-spectrum AED. It may be slightly less effective than carbamazepine in the treatment of focal-onset seizures but benefits from having fewer side effects. The commonest side effect is a rash, occurring in ~10% of patients. Its incidence is minimized by slowly titrating the dose to therapeutic levels.

Uses

Licensed uses

In the UK

- *Epilepsy*: lamotrigine is licensed for treatment as a monotherapy of focal-onset seizures and generalized seizures, including tonic–clonic seizures, in individuals aged 13 years and older and for treatment of absence seizures in individuals aged 2 years and older. As an adjunct, it is licensed for the treatment of focal-onset seizures, generalized seizures, including tonic–clonic seizures and seizures associated with LGS, in individuals aged 2 years and older.

In the USA

- *Epilepsy*: lamotrigine is licensed for treatment as a monotherapy of focal-onset seizures in individuals aged 16 years and older. Its use as a monotherapy is limited to second-line following conversion from one of the following AEDs: carbamazepine, phenobarbital, phenytoin, primidone, or valproate. As an adjunct, it is licensed for the treatment of focal-onset seizures, generalized seizures associated with LGS, and primary generalized tonic–clonic seizures in other epileptic patients in individuals aged 2 years and older.

Off-licence uses

- Neuropathic pain, prophylaxis of SUNCT, and trigeminal neuralgia.

Presentation

- *Trade names*: Lamictal® and Lamictal XR®. Generics are available.
- *Formulations*: lamotrigine is available as a dispersible and a standard tablet. Dispersible tablet: 5mg, 25mg, and 100mg. Standard tablet: 25mg, 50mg, 100mg, and 200mg.

Mechanism of action

The mechanism of action in epilepsy, neuropathic pain, and SUNCT is thought to be predominantly through blockade of voltage-gated sodium channels, thereby inhibiting neuronal depolarization and the transmission of both epileptic activity and nociceptive signals.

Toxicity and side effects

- *Common—dermatological*: rash occurs in up to 10% of patients and will resolve on withdrawal of the medication. It typically occurs in the first 8 weeks or if medication is suddenly stopped and resumed. The main concern is the development of Stevens–Johnson syndrome (see further text). Patients should be counselled about the risk of rash prior

to initiation of treatment. If a rash appears and there are no worrying features, i.e. it peaks quickly, settles in 2 weeks, is non-confluent and non-tender, and there are no associated clinical or biochemical features, then the medication can be reduced or held at the current dose. An antihistamine or a topical corticosteroid can be started, and the patient should be monitored closely for the development of new symptoms/spread of the rash. *Gastrointestinal*: diarrhoea, dry mouth, nausea, and vomiting. *Musculoskeletal*: back pain. *Neurological*: dizziness, fatigue, headache, insomnia, and tremor. *Ophthalmological*: blurred and double vision. *Psychiatric*: aggression and irritability.

- *Serious—dermatological*: the most serious consequence is the development of Stevens–Johnson syndrome or toxic epidermal necrolysis which has an incidence of 1/1000 in >12 years old. This risk is increased with: younger patients, concomitant use of valproate, rapid initiation of medication, and atopic individuals. It is now thought that the risk of serious skin rash is comparable to other medications, such as carbamazepine and phenytoin, which have traditionally been seen as safer. The rash may also rarely represent the beginning of a multiorgan hypersensitivity syndrome. *Gastrointestinal*: hepatic failure is very rare and usually, but not always, occurs within the context of a hypersensitivity reaction. *Haematological*: rarely, blood dyscrasias can occur, including anaemia, leucopenia, pancytopenia, and thrombocytopenia.

Contraindications

- *Absolute*: known hypersensitivity to lamotrigine or its excipients.
- *Relative*: lamotrigine may worsen myoclonic epilepsy. The dose should be reduced in hepatic dysfunction—50% of the dose should be used in moderate hepatic impairment, and 25% in severe hepatic impairment. Metabolites may also accumulate in renal failure; hence the maintenance dose should be reduced in severe renal impairment.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function, and benefit from lower dosing regimens. Co-prescription of other medications is also more likely in the elderly, and hence the risk of pharmacokinetic interactions is high.
- *Pregnancy*: animal studies have demonstrated some teratogenic side effects, but there have been no controlled trials in humans. Use in pregnancy involves weighing up the potential benefits and side effects. Lamotrigine plasma concentrations will decrease markedly during pregnancy by up to two-thirds; hence an increase in dose may be required.
- *Lactation*: lamotrigine enters maternal milk, and breastfed infants can have plasma levels 25–50% of maternal plasma levels. Infants should be monitored for potential side effects, such as fatigue and irritability, and an alternative feeding regimen used if these are identified.

Efficacy

- *Epilepsy*: the SANAD study—a large, unblinded RCT, based in the UK, concluded that lamotrigine had a longer time to treatment failure than all alternatives, except for oxcarbazepine, in the treatment of focal-onset epilepsy. The results suggested that lamotrigine and carbamazepine may have similar efficacy for focal-onset seizures, but that lamotrigine is more likely to be tolerated by patients. Valproate was found to be more effective than lamotrigine for generalized seizures.
- *SUNCT*: lamotrigine has been shown in case studies to be effective as a preventative agent in SUNCT syndrome and is the first-line agent for SUNCT prophylaxis.

For efficacy in neuropathic pain, see Chapter 5, Neuropathic pain.

Dosing and monitoring

Dosing

As a rule, uptitration of lamotrigine is performed slowly to reduce the incidence of side effects. If oral dosing is stopped for >5 days, then slow uptitration will need to be restarted.

- *Monotherapy of seizures*, age >12 years: start treatment with 25mg od. After 2 weeks, increase to 50mg/day in 1–2 divided doses; thereafter, lamotrigine can be increased by up to 100mg/day every 1–2 weeks. The normal maintenance dosage is between 100mg and 200mg in 1–2 divided doses, although dosages up to 500mg can be used.
- *Adjunctive therapy of seizures*, age >12 years: doses depend on whether it is used with valproate or enzyme-inducing drugs:
  - *for adjunctive use with valproate*: start treatment at 25mg on alternate days for 2 weeks, and then increase to 25mg daily for 2 weeks. Then it can be increased by 50mg/day every 1–2 weeks. The normal maintenance dose is 100–200mg daily;
  - *for adjunctive use without valproate but with enzyme-inducing drugs*: start treatment at 50mg od for 14 days. Increase to 50mg bd for a further 2 weeks, then increase by 100mg/day every 1–2 weeks up to 700mg daily. The normal maintenance dose is 200–400mg/day in two divided doses;
  - *for adjunctive use without valproate and without enzyme-inducing drugs*: start treatment at 25mg od for 2 weeks. Increase to 50mg/day in 1–2 divided doses for a further 2 weeks, then increase by a maximum of 100mg every 1–2 weeks. The normal maintenance dose is 100–200mg daily.
- *For SUNCT*: start treatment at 25mg/day, then increase in 25mg increments every 2 weeks. The final dose can range from 50mg to 600mg, depending on the response.

Routine monitoring Hepatic and renal function should be assessed prior to starting and yearly while treatment is ongoing.

Therapeutic drug monitoring Optimum seizure control, when used in monotherapy, occurs at plasma concentrations of 3–15mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is >95% but can be reduced by food co-ingestion. T_{max} is 1–3h, and plasma levels reach a steady state by 3–7 days. 90% of the lamotrigine dose is metabolized into inactive metabolites in the liver. Lamotrigine also undergoes autoinduction, so that clearance may increase by up to 37%, requiring an increase in dose. The half-life for lamotrigine varies dramatically, depending on whether valproate or enzyme-inducers are co-prescribed. In the absence of both, the half-life is between 15h and 35h. With valproate, the half-life is 30–90h; with enzyme inducers, it is 8–20h, and, with both valproate and enzyme inducers, it is 15–35h.

~100% of the medication is eliminated renally, 90% as inactive metabolites and the remaining 10% as unchanged drug.

Interactions See Table A.77.

Table A.77 Interactions of lamotrigine

Medications which alter lamotrigine plasma levels	Medications whose plasma levels are altered by lamotrigine
Levels decreased: carbamazepine, eslicarbazepine acetate, methsuximide, olanzapine, oral contraceptives, oxcarbazepine, paracetamol, phenobarbital, phenytoin, primidone, retigabine, rifampicin, rufinamide, and ritonavir	**Levels decreased:** clonazepam, levetiracetam, and valproate
Levels increased: valproate	**Levels increased:** retigabine

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Pareja J, Alvarez M, Montojo T. SUNCT and SUNA: recognition and treatment. *Curr Treat Options Neurol* 2013;**15**(1):28–39.

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Levetiracetam

Levetiracetam was first marketed in the UK as an AED in 2000. It is a useful broad-spectrum agent. It is very effective, and has simple pharmacokinetics and a relatively good side effect profile. It is a first-line AED in the treatment of focal-onset epilepsy with or without secondary generalization, and, in the UK, it is commonly used for primary generalized tonic–clonic seizures as well.

Uses

Licensed uses

In the UK

- *Epilepsy*: levetiracetam is licensed as a monotherapy for the treatment of focal-onset seizures with or without secondary generalization in individuals aged 16 years and older. As an adjunct, it is licensed in the treatment of focal-onset seizures with or without secondary generalization in individuals aged 1 month and older, as well as the treatment of myoclonic seizures associated with juvenile myoclonic epilepsy and primary generalized tonic–clonic seizures associated with idiopathic generalized epilepsy in individuals aged 12 years and older.

In the USA

- *Epilepsy*: levetiracetam is licensed for the treatment as an adjunct of focal-onset seizures in individuals aged 4 years and older, myoclonic seizures associated with juvenile myoclonic epilepsy in individuals aged 12 years and older, and primary generalized tonic–clonic seizures associated with idiopathic generalized epilepsy in individuals aged 6 years and older.

Off-licence uses

- Absence and myoclonic seizures, ET, and status epilepticus.

Presentation

- *Trade names*: Desitrend® and Keppra®. Generics are available.
- *Formulations*: levetiracetam is available as a concentrate for IV infusion, a film-coated tablet, and an oral solution. Concentrate for IV infusion: 100mg/mL. Film-coated tablet: 250mg, 500mg, 750mg, and 1g. Oral solution: 100mg/mL.

Mechanism of action

The exact mechanism of action of levetiracetam remains unclear. *In vitro* studies have demonstrated multiple possible mechanisms: (1) partial inhibition of N-type calcium channels, resulting in depletion of intraneuronal calcium; (2) it may act to increase GABA- and glycine-gated currents; and (3) some of its effects may be mediated by its binding to synaptic vesicle protein 2A—a compound important for neurotransmitter release.

Toxicity and side effects

- *Common—dermatological*: rash. *Gastrointestinal*: abdominal pain, anorexia, diarrhoea, dyspepsia, nausea, and vomiting. *Neurological*: fatigue and headache are very common. Ataxia, dizziness, seizures and

tremor are common. *Psychiatric*: aggression, anxiety, depression, and insomnia. *Respiratory*: cough and nasopharyngitis.
- *Serious—dermatological*: Stevens–Johnson syndrome and toxic epidermal necrolysis have been reported. *Gastrointestinal*: hepatic failure and pancreatitis have been reported. *Haematological*: rarely, pancytopenia can occur. *Psychiatric*: psychotic disorders and suicidal ideation have been reported.

Contraindications

- *Absolute*: hypersensitivity to levetiracetam or its excipients.
- *Relative*: levetiracetam is predominantly cleared by the renal system; hence dosage needs to be adjusted, depending on the eGFR. If the eGFR is between 50 and 79mL/min/1.73m^2, the recommended dose is 500–1000mg bd, with a maximum of 2g/day. If the eGFR is between 30 and 49mL/min/1.73m^2, the recommended dose is 250–750mg bd, with a maximum of 1.5g/day. If the eGFR is <30mL/min/1.73m^2, the recommended dose is 250–500mg bd, with a maximum of 1g/day. The dose should be halved if there is severe hepatic impairment with an eGFR <60mL/min/1.73m^2. No dosage changes are required in mild to moderate hepatic impairment.

Uses in special populations

- *Elderly*: levetiracetam is a useful first-line drug in the elderly, due to the low level of drug interactions and adverse events. A smaller dosage may be required because of age-related renal impairment.
- *Pregnancy*: animal studies have demonstrated some teratogenic side effects, but there have been no good-quality studies in humans. The plasma concentrations of levetiracetam can decrease by up to 60%; hence an increase in dose may be required. Use in pregnancy involves weighing up the potential benefits and side effects (see Antiepileptic drugs in young women, pp. 37–9).
- *Lactation*: levetiracetam enters maternal milk, and plasma levels in breastfed infants are <20% of maternal plasma levels. Monitor infants for potential side effects, such as fatigue and irritability, and switch to an alternative feeding regimen if these are identified.

Efficacy

As a monotherapy in the treatment of focal-onset epilepsy in adults, one double-blind trial showed 6-month seizure freedom in levetiracetam-treated patients was directly comparable to patients treated with carbamazepine. As an adjunct in the treatment of tonic–clonic epilepsy, an RCT demonstrated 72% of patients vs 45% with placebo had a 50% or greater reduction in seizure frequency.

For evidence in status epilepticus, see Status epilepticus, pp. 41–5.

Dosing and monitoring

Dosing

- *Monotherapy of focal-onset seizures*, age >16 years: start treatment at 250mg od. This should be increased in 1–2 weeks to 250mg bd, and then further increased by doses of 250mg bd in 2-week intervals to a maintenance dose of 1–3g/day in divided doses.

- *Adjunctive therapy of focal-onset seizures, and myoclonic and tonic–clonic seizures*, age >18 years and >50kg body weight: start treatment at 250mg bd, and increase by 500mg bd every 2–4 weeks to a maximum of 3g/day in divided doses.

Routine monitoring Renal function should be checked prior to starting treatment. Patients should be monitored for signs of depression and behavioural disturbance.

Therapeutic drug monitoring Optimum seizure control, when used in monotherapy, occurs at plasma concentrations of 12–46mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is almost 100% and is not affected by food co-ingestion. T_{max} is <2h. Steady state is achieved in 2 days. The compound demonstrates linear pharmacokinetics and 0% protein binding. Thirty per cent of levetiracetam will be metabolized to an inactive metabolite by a type-B esterase enzyme in whole blood. There is no autoinduction. Almost 100% of levetiracetam is eliminated by the kidneys, about two-thirds as the unchanged drug. The half-life is 6–8h in adults; this is increased to 10–11h in the elderly. The half-life is directly proportionate to renal CrCl.

Interactions See Table A.78.

Table A.78 Interactions of levetiracetam

Medications which alter levetiracetam plasma levels	Pharmacodynamic interactions
Levels decreased: carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, and phenytoin	**With carbamazepine, valproate, and topiramate:** may increase the likelihood of side effects **With CNS depressants, e.g. alcohol and MAOIs:** can enhance sedative side effects

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Levodopa

Levodopa was first used as an oral agent in the treatment of PD in 1967. It is the most effective medical treatment for PD, but long-term use is often complicated by motor fluctuations and dyskinesias.

Uses

Licensed uses

In the UK/USA

- *PD*: used for the treatment of PD at any stage of the disease process as monotherapy or in combination with other antiparkinsonian agents, in individuals aged 18 years and older. Duodopa® is licensed in the UK, but not the USA, for the treatment of advanced levodopa-responsive PD with severe motor fluctuations and hyper- or dyskinesia if the effects of other levodopa formulations are not sufficient.

Off-licence uses

- Dystonia, Parkinson's plus syndromes, and RLS.

Presentation

Levodopa is available as a combination therapy with a dopa decarboxylase inhibitor (DDI); benserazide (co-beneldopa) or carbidopa (co-careldopa). It is also available as a gel with carbidopa—as Duodopa® for the management of advance disease.

Co-beneldopa

- *Trade names*: Madopar® and modified-release Madopar® CR. Generics are available.
- *Formulations*: co-beneldopa is available as a dispersible tablet, a modified-release capsule and tablet, as well as a standard tablet. Dispersible tablet: 12.5/50mg and 25/100mg. Modified-release capsule: 12.5/50mg, 25/100mg, and 50/200mg. Modified-release tablet: 25/100mg. Standard tablet: 12.5/50mg, 25/100mg, and 50/200mg.

Co-careldopa

- *Trade names*: Parcopa®, Sinemet®, and modified-release Caramet® CR. Generics are available.
- *Formulations*: co-careldopa (carbidopa/levodopa) is available as a modified-release tablet and a standard tablet. Modified-release tablet: 25/100mg and 50/200mg. Standard tablet: 12.5mg/50mg, 10mg/100mg, 25mg/100mg, and 25mg/250mg.
- *Trade names*: Duodopa®. Generics are not available.
- *Formulations*: available as gel for enteral infusion 5/20mg/mL in a 100mL cassette.

Mechanism of action

Levodopa crosses the blood–brain barrier to be converted to dopamine. This replaces dopamine lost due to death of nigrostriatal dopaminergic neurons in PD. It is always used in conjunction with a DDI (carbidopa or benserazide). DDIs do not cross the blood–brain barrier and act to prevent the peripheral conversion of levodopa to dopamine. This results in greater concentration of levodopa reaching the brain, as well as reduces side effects that result from peripherally acting dopamine (nausea and vomiting).

Toxicity and side effects

- *Common—cardiovascular*: postural hypotension.
  Gastrointestinal: anorexia, nausea, and vomiting. Antiemetics with central antidopaminergic action should be avoided, e.g. phenothiazines.
  Neurological: dyskinesias (60% of patients after long-term therapy. This appears to be dependent on the dose, duration, and onset age, with younger patients usually affected sooner). On–off phenomenon (periods of akinesia and improved mobility with dyskinesias) after prolonged therapy. *Psychiatric*: agitation, anxiety, confusion, depression, hallucinations, insomnia, and somnolence.
- *Serious—cardiovascular*: arrhythmias (rare), e.g. ventricular extrasystoles and AF. *Neurological*: sudden-onset sleep.

Contraindications

- *Absolute*: angle-closure glaucoma, severe psychosis or deterioration in psychiatric illness after commencement, and patients using non-selective MAOIs.
- *Relative*: no dose alteration is required in hepatic or renal impairment.

Uses in special populations

- *Elderly*: levodopa is considered safe in the elderly; no dose adjustment is required.
- *Pregnancy*: teratogenicity was noted in animal studies. Use in pregnancy if benefits outweigh the risks.
- *Lactation*: levodopa is excreted into breast milk and also inhibits lactation. Manufacturers do not advise use while breastfeeding.

Efficacy

The efficacy of levodopa in the treatment of PD has been known since 1961 and shown in several high-quality trials. It still remains the gold standard of treatment. The *ELLDOPA* (Early versus Late Levodopa in PD) study was a double-blind RCT designed to assess long-term effects of levodopa. It assigned patients with untreated PD (n = 361) to either 150mg, 300mg, or 600mg of levodopa or placebo for 40 weeks with a 2-week withdrawal period. Patients treated with levodopa demonstrated a significant improvement in their UPDRS scores, compared to placebo, and higher doses were associated with an increased risk of dyskinesia. Retrospective analyses of the study suggest that, although levodopa significantly improved PD signs, compared to placebo, there was a wide range of clinical responses to treatment and that patients in the early stages of PD did not experience as robust a response to levodopa.

Dosing and monitoring

1. *PD*.

Dosing

Start treatment at 50–100mg of levodopa bd to tds. This can be increased by 100mg of levodopa daily to a usual maintenance dose of 100mg of levodopa tds. If response is insufficient, doses of 1000mg or more daily (if tolerated) should be considered, with some experts advocating up to 2000–3000mg. However, the aim is to use the lowest effective dose. Nausea and vomiting experienced by many patients commenced on levodopa may be treated with domperidone (20mg bd to tds), for as short a time as possible due to concern of cardiac side effects.

Duodopa® is used where other treatments have failed or with severe motor fluctuations. The manufacturer advises a morning bolus equivalent to the patient's usual morning levodopa dose infused over 10–30min. This is followed by a maintenance infusion of the patient's daily levodopa dose over 16h. Bolus doses (0.5–2mL) are used for periods of hypokinesia. If >5 boluses are needed, the maintenance dose should be increased.

Gradual dose reduction is advised when treatment is being discontinued, in order to avoid NMS and DAWS. Where patients are temporarily unable to take oral medication (e.g. preoperatively), an alternative route of dopamine administration should be used (e.g. DA by transdermal patch).

2. *RLS*.

Dosing

- Immediate-release tablet: 12.5–25mg (0.5–1 tablet) given in the evening, at bedtime, or upon waking during the night with RLS symptoms.
- Controlled-release tablet: 25mg (one tablet) before bedtime for RLS symptoms that awaken the patient during the night.

Monitoring Monitor for onset of motor complications in PD and augmentation in RLS.

Pharmacokinetics and interactions

Pharmacokinetics

There is significant inter-person variability in the absorption of levodopa. Oral bioavailability of levodopa is 98% (extended-release 75%). T_{max} is 1–2h. Increased protein intake lowers absorption across the gut and movement across the blood–brain barrier. Administration with a peripheral DDI increases the amount of levodopa crossing the blood–brain barrier from 1–3% to 10%. Levodopa and DDIs are 10–30% protein-bound. Levodopa is metabolized primarily through decarboxylation by aromatic amino acid decarboxylase. This is present in a range of peripheral tissues, including the intestine, kidneys, liver, and spleen, as well as the brain. This produces dopamine which is metabolized further to 3,4-dihydroxyphenylacetic acid (DOPAC) and subsequently to inactive homovanillic acid (HVA). The half-life of levodopa is 1.5h when administered with a DDI. Eighty per cent of the dose is excreted renally as its metabolites (DOPAC and HVA).

The pharmacokinetic profile of Duodopa® is similar to that of other preparations. However, the morning bolus allows for therapeutic concentrations to be reached in 10–30min, and there is significantly less fluctuation in plasma concentrations (and hence theoretically a reduction in the occurrence of motor fluctuations, when compared to traditional oral preparations).

Interactions See Table A.79.

Table A.79 Interactions of levodopa

Medications which alter levodopa plasma levels	Pharmacodynamic interactions
Levels decreased: anticholinergics, pyridoxine, and TCAs	**With non-selective MAOIs:** may cause hypertensive crises
Levels increased: antacids	**With antihypertensives:** may cause orthostatic hypotension

References

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Lidocaine

In the context of neurology, lidocaine is most commonly used as a patch in the management of post-herpetic neuralgia; off-licence, it has also been used since the 1980s as an adjunct in the treatment of cluster headache and acute episodes of SUNCT. The effects of lidocaine on cluster headache are modest, and it is best used when patients have not responded to more conventional agents.

Uses

Licensed uses

In the UK/USA

- *Post-herpetic neuralgia*: lidocaine patches are licensed topically for post-herpetic neuralgia in individuals aged 18 years and older.

Off-licence uses

- Allodynia (patch), cluster headache (intranasal), and SUNCT (IV).

Presentation

- *Trade names*: Laryngojet®, Lidoderm®, LTA 360 Kit®, Versatis®, and Xylocaine®. Generics are available.
- *Formulations*: lidocaine is available in a number of different formulations. In neurology, it is used in the management of cluster headache as an intranasal spray, in post-herpetic neuralgia as a patch, and in SUNCT as an IV infusion. Intranasal spray: lidocaine 4% (4mg/mL) and lidocaine 10% (10mg/mL) concentrations in 4mL and 50mL bottles, respectively. IV infusion: 1% and 2% w/v in 2mL, 5mL, 10mL, and 20mL ampoules. Patch: 5% w/w lidocaine.

Mechanism of action

Lidocaine acts by blocking neuronal voltage-gated sodium channels, hence reducing neuronal activation. The effect of lidocaine on TACs is thought to be via inhibition of neuronal activation in the sphenopalatine ganglion, an area believed to be involved in the pathogenesis of cluster headache. In post-herpetic neuralgia, it is believed to act locally by reducing the activity of nociceptive neurons.

Toxicity and side effects

In the doses used for cluster headache and post-herpetic neuralgia, side effects are few, typically localized, and, unlike when used as an IV infusion, systemic toxicity is uncommon.

- *Common—cardiac*: hypotension. *Dermatological*: erythema, local irritation, oedema, petechiae. *Gastrointestinal*: nausea and vomiting. *Neurological*: confusion, drowsiness, headache, paraesthesiae.
- *Serious—cardiac*: arrhythmias, bradycardia, cardiorespiratory arrest. *Haematological*: methaemoglobinaemia. *Immunological*: anaphylaxis. *Neurological*: coma, convulsions, malignant hyperthermia.

Contraindications

- *Absolute*: acute porphyria, congestive heart failure, previous hypersensitivity, second- and third-degree heart block with no pacemaker, sinoatrial disease, Wolff–Parkinson–White syndrome.

- *Relative*: use with caution in hepatic and renal impairment, due to increased risk of adverse effects. Dose adjustment is not usually required.

Uses in special populations

- *Elderly*: the lidocaine patch is usually well tolerated in the elderly, however the intravenous formulation should be used only with significant caution as they are more prone to toxicity due to an age-related decline in renal and hepatic function and are more likely to suffer from cardiac disease.
- *Pregnancy*: lidocaine has not been shown to be harmful during pregnancy in animal studies, and there are no confirmed reports of teratogenicity in humans. It should only be used if benefits outweigh risks.
- *Lactation*: lidocaine is present in breast milk, but the amount is considered too small to be harmful.

Efficacy

- *Neuropathic pain*: a systematic review found three studies, involving 314 patients with post-herpetic neuralgia treated with topical lidocaine. All studies found a beneficial effect, and a meta-analysis of two of the studies found a statistically significant effect for lidocaine vs placebo for secondary outcome measures (mean improvement in pain scores of 0.42 on a 10-point scale, 95% CI 0.14–0.69; $p = 0.003$). The authors concluded that there is still insufficient evidence to recommend topical lidocaine as first line in the treatment of any neuropathic pain syndrome. NICE guidance agrees with this conclusion and only recommends topical lidocaine in the treatment of localized neuropathic pain in patients unable to tolerate or use oral medications. Notably, the EFNS recommends topical lidocaine as first-line treatment for post-herpetic neuralgia in elderly patients.
- *TACs*: there are limited data on the efficacy of intranasal lidocaine in aborting cluster headache attacks. One open-label study of 30 male patients with cluster headache who were given 4% lidocaine intranasally found that 54% experienced some relief. The only RCT of intranasal lidocaine looked at nine patients with cluster-like headaches induced with nitroglycerin and subsequently treated with intranasal cotton wool swabs soaked in either 10% cocaine hydrochloride, 10% lidocaine, or saline. Patients were pain-free with cocaine after 31.3 ± 13.1min, and with lidocaine after 37.0 ± 7.8min. With placebo, there was an increase in headache severity after application, and time to recovery was 59.3 ± 12.3min. IV lidocaine has been shown in case reports to have some efficacy in the termination of SUNCT attacks. Freedom from attacks may only be maintained for the duration of the infusion.

Dosing and monitoring

Dosing

- *Cluster headache*: the dose advised is 1mL of lidocaine (4–10%) in the ipsilateral nostril, given as a spray or as a drop. Repeat dosing should be avoided.
- *Post-herpetic neuralgia*: apply patches, as required, to the affected area for a maximum of 12h each day. Assess whether there has been benefit from treatment after a minimum of 2 weeks.
- *SUNCT*: a loading dose of 1mg/kg can be given (optional). The maintenance dose is 1–4mg/kg/h IV, given for a maximum of 7 days.

Routine monitoring Routine monitoring is not needed for the nasal spray or topical patch. Patients should have an ECG done and liver and renal function checked before starting the infusion. Continuous cardiac monitoring and regular BP monitoring should be in place during infusions.

Pharmacokinetics and interactions

Pharmacokinetics

Lidocaine is absorbed rapidly and extensively when given topically. The rate and extent of absorption are variable, depending on the concentration, site of application, and length of exposure. It undergoes extensive first-pass metabolism by the liver where it is de-ethylated to form the active metabolites monoethylglycinexylidide and glycinexylidide. These metabolites have a half-life of 2h and 10h, respectively, and, although active, they are less potent than lidocaine, which has a half-life of 1.5–2h. 60–80% of the drug is protein-bound. Metabolism is predominantly hepatic. Less than 10% of unchanged lidocaine is excreted by the kidneys.

Interactions See Table A.80.

Table A.80 Interactions of lidocaine

Medications which alter lidocaine plasma levels	Pharmacodynamic interactions
Levels increased: cimetidine and protease inhibitors	**With agents causing hypokalaemia:** reduced efficacy of lidocaine with hypokalaemia **With anti-arrhythmics:** increased risk of arrhythmias **With antipsychotics:** risk of prolonged QT **With β-blockers and other local anaesthetics:** can cause myocardial depression

References

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Lomustine

Lomustine was first licensed in the 1970s for the treatment of brain tumours. It is one of a class of alkylating agents called the nitrosoureas. It benefits from being markedly lipophilic, allowing rapid diffusion across the blood–brain barrier. Its main limitations are a delayed myelosuppressive effect and a cumulative toxic impact on renal and pulmonary function. It is mainly used as a single agent or in combination with procarbazine and vincristine (PCV) for the treatment of recurrent high-grade glioma.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- *Brain tumours*: lomustine is licensed for use in the management of both primary and metastatic brain tumours, usually in combination with radiotherapy ± surgery, in individuals of all ages.

Off-licence uses

- None.

Presentation

- *Trade names*: CCNU®. Generics are available.
- *Formulations*: lomustine is available as a 10mg, 40mg, and 100mg capsules (only available as 40mg in the UK).

Mechanism of action

Lomustine is a cell cycle non-specific alkylating agent that acts by forming cross-links in both DNA and RNA. This inhibits DNA and protein synthesis. Part of its action may also be mediated by carbamoylation of amino acids.

Lomustine is highly lipid-soluble at physiological pH, allowing it to rapidly distribute across the blood–brain barrier.

Toxicity and side effects

The commonest adverse effect is myelosuppression. This is often delayed and dose-related. Thrombocytopenia occurs at 4 weeks and lasts 1–2 weeks. Leucopenia <5000 white blood cells (WBCs)/mm^3 occurs in 65% at 5–6 weeks. Anaemia is less common and less severe.

- *Common—gastrointestinal*: anorexia, nausea, and vomiting.
- *Serious—haematological*: acute leukaemia, bone marrow failure, and bone marrow dysplasia. *Ophthalmological*: irreversible visual loss can rarely occur if used with radiation. *Renal*: progressive renal failure has been reported in patients with high cumulative doses; hence the maximum recommended lifetime total dose is 1000mg/m^2. *Respiratory*: interstitial pneumonia and lung fibrosis (delayed onset has been reported up to 6 months with lomustine, and up to 17 years post-treatment with other nitrosoureas).

Contraindications

- *Absolute*: previous hypersensitivity to nitrosoureas, coeliac disease, severe bone marrow depression, and severe renal impairment.
- *Relative*: reduced pulmonary function at baseline. Men should be warned about the possibility of permanent infertility. Lomustine is hepatically metabolized; hence caution should be used in hepatic impairment.

Uses in special populations

- *Elderly*: no clinical studies have looked directly at the use of lomustine in those over 65 years old. The elderly have an age-related deterioration in their renal and hepatic function, and benefit from lower dosing regimens.
- *Pregnancy*: lomustine is teratogenic and embryotoxic in animal studies. Women of childbearing age should be offered contraception and advised to avoid becoming pregnant.
- *Lactation*: lomustine levels within breast milk is unknown. The drug is lipophilic and hence is likely to transfer to the newborn in this manner. Mothers should be given advice about the benefits of breastfeeding vs the potential adverse effects of the drug, and offered alternative methods of feeding.

Efficacy

Lomustine is commonly used in combination with procarbazine and vincristine, as part of PCV chemotherapy. A meta-analysis of 18 studies conducted in 1993 estimated that combined radiation and chemotherapy was associated with an increased survival of 10.1% at 1 year and 8.6% at 2 years, compared to radiotherapy alone. In contrast, a large RCT looking at the same question showed no significant difference in median survival between radiotherapy and radiotherapy with PCV (9.5 vs 10 months, respectively).

Response rates for nitrosourea-based chemotherapy for the management of recurrent anaplastic astrocytoma and glioblastoma multiforme vary but are estimated to range between 8% and 27%.

Dosing and monitoring

Dosing

The dosage of lomustine varies, depending on the body surface area (BSA), bone marrow status, clinical indication, local protocols, and other adjuvants used in the chemotherapy regimen. Readers are advised to follow local guidelines.

For use as a single agent in treatment-naïve patients without bone marrow depression, the initial dose is typically 120–130mg/m^2. Patients usually recieve a single oral dose every 6–8 weeks. The dose is then adjusted, based on haematological parameters. Repeat doses should only be given if the platelet count is >100 000/mm^3 and leucocytes >4000/mm^3.

Routine monitoring Prior to initiation of treatment, FBC, and renal, liver, and pulmonary function should be assessed. An FBC is recommended once weekly for at least 6 weeks post-dose. Liver, pulmonary, and renal function should be assessed regularly during treatment.

Pharmacokinetics and interactions

Pharmacokinetics

The bioavailability of lomustine is difficult to assess, as it rapidly decomposes in the gastrointestinal tract, with no intact drug detectable in the plasma, following oral administration. Lomustine decomposes to multiple metabolites, including cyclohexylamine, cyclohexylisocyanate, and N,N′-dicyclohexylurea. The relative pharmacological activity of these metabolites is unknown. T_{max} occurs at 1–4h. The metabolites are highly lipophilic, allowing rapid diffusion across the blood–brain barrier and CSF levels of 30% plasma levels.

The half-life ranges from 4h to 72h, depending on the metabolite. The details of further metabolism of lomustine metabolites are unknown. In trials using radiolabelling, 60% of radioactivity is excreted in the urine by 48h, with the majority of the rest excreted by 72h and <5% excreted in faeces.

Interactions See Table A.81.

Table A.81 Interactions of lomustine

Medications which alter lomustine plasma levels	Pharmacodynamic interactions
Levels decreased: phenobarbital	With other chemotherapeutic agents, **cimetidine, clozapine, and theophylline**: may increase severity of myelosuppression

References

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Low-molecular-weight heparin, e.g. tinzaparin

Tinzaparin was first marketed in the UK in 1993 and is one of numerous preparations of LMWHs used globally. Other commonly used preparations include dalteparin, enoxaparin, and nadroparin.

Uses

Licensed uses

In the UK/USA

- LMWHs are licensed for the treatment of deep vein thrombosis and pulmonary embolism in individuals aged 18 years and older.

Off-licence uses

- Cerebral venous sinus thrombosis.

Presentation

- *Trade names*: Innohep®. Generic forms are not available.
- *Formulations*: tinzaparin is available as 10 000iu/mL and 20 000iu/mL pre-filled syringes.

Mechanism of action

Tinzaparin is an antithrombotic agent. It potentiates the inhibition of several activated coagulation factors, especially factor Xa, its activity being mediated via antithrombin III.

Toxicity and side effects

See Unfractionated heparin, pp. 617–18.

Contraindications

See Unfractionated heparin, pp. 617–18.

Uses in special populations

See Unfractionated heparin, pp. 617–18.

- *Elderly*: no dose reduction required; however, the elderly experience an age-related impairment in renal function; hence regular monitoring of renal function is required.

Efficacy

- *Cerebral venous sinus thrombosis*: a Cochrane review conducted by Coutinho *et al*. in 2012 highlighted the paucity of evidence regarding the use of anticoagulation in cerebral venous thrombosis. It highlighted that several small RCTs have shown that early anticoagulation is effective, and thus obtaining ethical approval for larger, more robust studies has not been considered appropriate. Based upon the limited evidence available, anticoagulant treatment for cerebral venous sinus thrombosis is both safe and associated with a potentially important (although not statistically significant) reduction in the risk of mortality and neurological morbidity. Limited data suggest that LMWH is more effective than unfractionated heparin and at least as safe for the treatment of cerebral venous sinus thrombosis. LMWH may also be preferred due to ease of monitoring.

Dosing and monitoring

Dosing

For the treatment of cerebral venous sinus thrombosis, the LMWH should be administered at treatment dose. For tinzaparin, this is 175 units/kg od.

Monitoring Platelet counts should be measured in patients receiving LMWH treatment for longer than 5 days, and the treatment should be stopped immediately in those who develop thrombocytopenia.

Pharmacokinetics and interactions

Pharmacokinetics

Tinzaparin has a bioavailability of around 90%, following an SC injection. The absorption half-life is 200min, with peak plasma activity being observed after 4–6h. The elimination half-life is about 90min. Tinzaparin is primarily renally excreted.

Interactions See Unfractionated heparin, pp. 617–18.

Melatonin

Melatonin standard and modified-release formulations have variable licensing status worldwide. In the USA, they are termed a dietary supplement, while, in the UK, use requires a prescription. A melatonin prolonged-release formulation Circadin® was first marketed in the UK in 2008. It is indicated primarily for the treatment of primary insomnia in the >55 year olds, although off-licence uses have seen it trialled in a variety of sleep disorders. It has modest efficacy in the treatment of primary insomnia and a relatively benign side effect profile.

Uses

Licensed uses

In the UK

- *Insomnia*: a melatonin prolonged-release formulation (Circadin®) is licensed for use as monotherapy in the short-term treatment of primary insomnia typified by poor-quality sleep in patients aged 55 years and older.

In the USA

Melatonin is regulated through the FDA's Dietary Health and Education Act as a 'dietary supplement'; hence it can be purchased by individuals of any age and does not require a prescription.

Off-licence uses

- Circadian rhythm sleep disorders and RBD.

Presentation

- *Trade names*: Circadin®. Generics of this formulation are not available.
- *Formulations*: melatonin prolonged-release is available as a 2mg tablet.

Mechanism of action

Melatonin is an endogenous hormone which acts at melatonin receptors 1–3. It is secreted by the pineal gland during darkness, peaking at 2–4 a.m. It is believed to regulate the body's circadian rhythm. There is an age-related decline in melatonin secretion. Hence it is believed that, in the >55 year olds, exogenous melatonin tops up endogenous levels, preventing primary insomnia.

Toxicity and side effects

Melatonin is a relatively safe drug; side effects are uncommon. In clinical trials, the commonest side effects of arthralgia, back pain, headache, and nasopharyngitis were seen at similar levels in placebo groups.

- *Serious—dermatological*: cases of angio-oedema have been reported.

Contraindications

- *Absolute*: hypersensitivity to melatonin and lactose intolerance.
- *Relative*: no data are available with regard to use in autoimmune disorders, and hepatic or renal impairment; hence the manufacturer advises against use in autoimmune disorders and hepatic impairment (the latter due to the fact that clearance will be markedly reduced in these individuals) and advises caution if used in renal impairment.

Uses in special populations

- *Elderly*: melatonin is primarily indicated for the elderly population. Melatonin bioavailability and metabolism reduce with age.
- *Pregnancy*: animal studies have not demonstrated harmful effects in pregnancy. However, there are no clinical data with regard to melatonin use in human pregnancies; hence the manufacturer recommends avoidance in pregnancy.
- *Lactation*: as endogenous melatonin is present in human breast milk, exogenous melatonin is also likely to be present. There are no studies exploring the effects of increased melatonin levels on the infant, and hence the manufacturer has stated that it cannot recommend its use in breastfeeding mothers.

Efficacy

A number of RCTs have looked at the use of prolonged-release melatonin in the treatment of primary insomnia in >55 year olds. One of the latest studies published in 2009 demonstrated that 50% of individuals treated with prolonged-release melatonin had substantial improvement in sleep quality vs 15% with placebo. With regard to melatonin use in other primary sleep disorders, a meta-analysis conducted in 2013 investigated the use of melatonin for primary sleep disorders (including circadian rhythm disorders, insomnia, and RBD) in all ages. Overall, melatonin reduced sleep latency by 7.06min (95% CI 4.37–9.75) and increased total sleep time by 8.25min (95% CI 1.74–14.75). These effects did not diminish with continued use.

A further meta-analysis conducted in 2006 looked at the effects of melatonin for secondary sleep disorders. Analysis of 15 RCTs showed no evidence that melatonin had any effect on sleep onset latency.

Dosing and monitoring

Dosing

Start treatment at 2mg od ~1h prior to sleep. This can be used for up to 13 weeks. No rebound effects have been identified on stopping treatment.

Routine monitoring No routine monitoring is required.

Pharmacokinetics and interactions

Pharmacokinetics

The exact bioavailability of melatonin from Circadin® is unknown. In other oral formulations of melatonin, it is ~15% due to substantial first-pass metabolism. This figure is halved in the elderly. Peak plasma concentration occurs at 1.6h. Co-digestion with food delays this by 1h. Melatonin is 60% protein-bound. The half-life of Circadin® is 3.5–4h. It is predominantly metabolized hepatically by CYP1A1-2, and potentially CYP2C19, enzymes, into sulfated and glucuronide conjugates. The predominant metabolite, a sulfated conjugate, is inactive. Metabolites are excreted by the renal tract; <2% is excreted as unchanged melatonin.

Interactions See Table A.82.

Table A.82 Interactions of melatonin

Medications which alter melatonin plasma levels	Medications whose plasma levels are altered by melatonin	Pharmacodynamic interactions
Levels decreased: CYP1A2 inducers, e.g. carbamazepine, nicotine, and rifampicin **Levels increased:** CYP1A2 inhibitors, e.g. cimetidine, fluvoxamine, and oestrogen-containing compounds	**Levels decreased:** melatonin induces CYP3A *in vitro*; hence plasma concentrations of other medications metabolized by this enzyme may fall	**With alcohol:** reduced impact of Circadin® on sleep **With hypnotics, e.g. benzodiazepines, and Z-drugs, e.g. zopiclone:** increased sedative properties

References

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Memantine

Memantine was licensed for the treatment of AD in the UK in 2002. It is the only agent licensed for the symptomatic management of dementia that is not a cholinesterase inhibitor. It is thought to have a better side effect profile than cholinesterase inhibitors.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- *AD*: memantine is licensed for the symptomatic treatment of moderate to severe AD in individuals aged 18 and older.

In the UK, NICE recommends use in moderate disease only when patients are intolerant to, or have a contraindication to, AChEIs.

Off-licence uses

- DLB, mild to moderate VaD, and combination therapy with donepezil in the management of AD.

Presentation

- *Trade names*: Ebixa®, Maruxa®, Memantine Accord®, Namenda®, Namenda XR®, and Nemdatine®. Generics are not available.
- *Formulations*: memantine is available as an extended-release tablet, an oral solution, and a standard tablet. Extended-release tablet: 7mg, 14mg, 21mg, and 28mg. Oral solution: 2mg/mL (USA) and 10mg/mL (UK). Standard tablet: 5mg, 10mg, 15mg, and 20mg.

Mechanism of action

Memantine is a voltage-dependent, moderate-affinity, non-competitive *N*-methyl-D-aspartate receptor antagonist. This receptor controls synaptic plasticity and memory function. Memantine inhibits the prolonged influx of calcium ions from extrasynaptic receptors that result in neuronal excitotoxicity. Memantine is also a non-competitive 5HT3 antagonist (effect unknown) and an antagonist at α-7 nicotinic AChRs (may contribute to worsening seen in early treatment with memantine).

Toxicity and side effects

- *Common—cardiovascular*: hypertension. *Gastrointestinal*: constipation and deranged LFTs. *Immunological*: drug hypersensitivity. *Neurological*: disorders of balance, dizziness, and headache. *Psychiatric*: somnolence. *Respiratory*: dyspnoea.
- *Serious—cardiovascular*: cardiac failure, thromboembolism including venous thrombosis. *Gastrointestinal*: pancreatitis has been reported. *Neurological*: seizures. *Psychiatric*: psychosis has been reported.

Contraindications

- *Absolute*: hypersensitivity to memantine or its excipients, CrCl <5mL/min.
- *Relative*: caution in patients with cardiovascular disease and previous history of seizures. The dose should be adjusted in renal impairment. For the oral solution and standard tablet in moderate impairment (CrCl 30–49mL/min), the usual maintenance dose should be 10mg daily, increasing to 20mg only if well tolerated after at least 7 days' treatment. In severe impairment (CrCl 5–29mL/min), 10mg/day is the maximum recommended dose. A maximum dose of 14mg/day is recommended for the extended-release preparation in severe impairment. No dose adjustment is required in mild to moderate impairment. In hepatic impairment, all formulations of memantine are safe, in Child-Pugh grade A and B liver cirrhosis, without dose adjustment, but there are no data in Child–Pugh grade C cirrhosis where use is not recommended.

Uses in special populations

- *Elderly*: no dose adjustment is required in this group.
- *Pregnancy*: intrauterine growth retardation has been reported in animal studies. There are no existing reports of the effect of memantine use in pregnant humans, and therefore it should only be used if benefits outweigh risks.
- *Lactation*: it is not known if memantine is present in breast milk; however, it is highly lipophilic, suggesting that it probably is. The manufacturer advises avoidance in breastfeeding mothers.

Efficacy

- *AD*: a 2006 Cochrane review conducted a meta-analysis of RCTs investigating the use of memantine in patients with AD, VaD, and mixed dementia. In patients with moderate to severe AD, memantine showed significant benefits on cognition (2.97 points on the 100-point severe impairment battery score, 95% CI 1.68–4.26; p <0.0001), activities of daily living (1.27 points on the 54-point Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) severity score, 95% CI 0.44–2.09; p = 0.003), behaviour (2.76 points on the 144-point Neuropsychiatric Inventory (NPI) score, 95% CI 0.88–4.63; p = 0.004), and clinical impression of change (0.28 points on the 7-point Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) score, 95% CI 0.15–0.41; p <0.0001) after 6 months of treatment. Therefore, it is recommended for the treatment of moderate to severe AD.

  In the *DOMINO-AD* trial (Donepezil and Memantine in Moderate to Severe Alzheimer's Disease), an RCT of 295 patients with moderate to severe AD which investigated whether combination therapy with donepezil and memantine would be beneficial, it was established that dual therapy did not confer statistically significant additive benefits in cognitive or global outcomes, compared with donepezil alone.

- *Other forms of dementia*: in the same Cochrane review mentioned above, data pooled from two RCTs of 20mg/day of memantine in patients with mild to moderate VaD showed a small beneficial effect on cognition (1.85 ADAS-Cog points, 95% CI 0.88–2.83; $p = 0.0002$), as well as significantly less disturbed behaviour and reduced agitation. However, there was no significant effect on global clinical outcomes. As such, some clinicians advocate the use of memantine off-licence in patients with mild to moderate VaD. There is no strong evidence to advocate the use of memantine in PDD or DLB.

Dosing and monitoring

Dosing

For the oral solution and standard tablet, start treatment at 5mg od. This can be increased by 5mg in 1-week intervals up to a maximum dose of 20mg daily. Doses of >5mg/day should be given in divided doses. When using memantine for mild to moderate VaD (off-licence), the immediate-release preparation is advised, with a similar dosing and titration strategy as for AD.

For the extended-release preparation, start treatment at 7mg od, and increase by 7mg in weekly intervals to a recommended maintenance dose of 28mg od.

Routine monitoring Activities of daily living, behaviour, bowel function, cognitive function, and mood should be monitored while on treatment.

Pharmacokinetics and interactions

Pharmacokinetics

Memantine has a bioavailability of ~100%. Peak plasma concentrations are reached at 3–7h for immediate-release preparations, and 9–12h for extended-release preparations. This is not affected by ingestion of food. 45% of memantine is plasma protein-bound. Memantine undergoes partial hepatic metabolism into an *N*-glucuronide conjugate, 6-hydroxy memantine, and 1-nitroso-deaminated memantine, independent of the cytochrome P450 system. 48% of the total dose is excreted unchanged in the urine. The rest is eliminated as inactive metabolites predominantly by the renal tract. The terminal half-life is 60–80h.

Interactions See Table A.83.

Table A.83 Interactions of memantine

Medications which alter memantine plasma levels	Medications whose plasma levels are altered by memantine	Pharmacodynamic interactions
Levels increased: carbonic anhydrase inhibitors, cimetidine, nicotine, procainamide, ranitidine, quinidine, quinine, sodium carbonate, and trimethoprim	**Levels decreased:** hydrochlorothiazide **Levels increased:** warfarin	**With trimethoprim:** may cause myoclonus and delirium **With levodopa, dopaminergic agonists, and anticholinergics:** effects of these medications may be increased

References

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Tan C, Yu J, Wang H, Tan M, *et al*. Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis* 2014;**41**(2):615–31.

Methotrexate

Methotrexate was initially used as a chemotherapeutic agent in acute lymphoblastic leukaemia in the 1950s. A role in treating rheumatoid arthritis was established in the 1970s, and it is now also used in a wide range of autoimmune neurological diseases.

Uses

Licensed uses

In the UK

- *Neuro-oncology*: methotrexate is licensed for use in a range of neoplastic conditions, including acute leukaemia, non-Hodgkin's lymphoma, sarcoma, and solid tumours of the breast, lung, head, and neck, among other neoplasms, in individuals of all ages.

In the USA

- *Neuro-oncology*: methotrexate is licensed for use in acute lymphoblastic meningeal leukaemia, trophoblastic neoplasms, breast, lung, and head and neck cancer, non-Hodgkin's lymphoma, among other neoplasms, in individuals of all ages.

Off-licence uses

- Behçet's.
- GCA.
- IBM (trial of therapy).
- MG (second-line, chronic).
- Neurolupus (first-line, chronic).
- NMO (second-line).
- Neurosarcoidosis.
- PM/DM (first-line, chronic).
- PCNSL.
- Sjögren's syndrome.
- Vasculitis (first-line, chronic).

Presentation

- *Trade name*: Maxtrex®, Metoject®, Rheumatrex®, and Trexall®. Generics are available.
- *Formulation*: methotrexate is available as an oral tablet, (Maxtrex®, Rheumatrex®, and Trexall®), a pre-filled syringe for injection (Metoject®), and a vial for injection. Oral tablet: 2.5mg, 5mg, 7.5mg, 10mg, and 15mg. Pre-filled syringe (50mg/mL): 0.15mL, 0.2mL, 0.25mL, 0.3mL, 0.35mL, 0.4mL, 0.45mL, 0.5mL, 0.55mL, and 0.6mL. Vial (2.5mg/mL): 2mL. Vial (25mg/mL): 2mL, 4mL, 8mL, 10mL, and 20mL. Vial (100mg/mL): 10mL and 50mL. Of note, only the 25mg/mL solution for injection is suitable for intrathecal administration; other doses are hypertonic and should not be administered in this fashion.

Mechanism of action

Methotrexate competitively inhibits dihydrofolate reductase. This enzyme converts folate into tetrahydrofolic acid, a substrate required for DNA synthesis. This action inhibits DNA synthesis and therefore cellular replication, giving antineoplastic and immunosuppressant effects.

Toxicity and side effects

- *Common—endocrine*: impotence and loss of libido. *Gastrointestinal*: abdominal pain, nausea, and ulcerative stomatitis. *Haematological*: leucopenia. *Immunological*: vasculitis. *Ophthalmological*: conjunctivitis.
- *Serious—cardiovascular*: pericarditis and thromboembolic events. *Dermatological*: Stevens–Johnson syndrome and toxic epidermal necrolysis. *Gastrointestinal*: gastrointestinal ulceration/bleeding, hepatic impairment (including acute necrosis and fibrosis), malabsorption, pancreatitis, and toxic megacolon. *Genitourinary*: acute kidney injury and defective oogenesis/spermatogenesis. *Gynaecological*: vaginal ulceration. *Haematological*: anaemia, bone marrow failure, hypogammaglobulinaemia, and thrombocytopenia. *Immunological*: increased risk of infections. *Neurological*: leukoencephalopathy and stroke. *Respiratory*: acute or chronic interstitial pneumonitis and pulmonary fibrosis or oedema.

Contraindications

- *Absolute*: hypersensitivity, active infections, immunodeficiency syndromes, significant renal or hepatic impairment, and significant anaemia, leucopenia, or thrombocytopenia.
- *Relative*: reduced doses of methotrexate should be used in patients with mild renal impairment. Caution and regular monitoring of LFTs are required in pre-existing hepatic impairment.

Use in special populations

- *Elderly*: the elderly experience an age-related decline in hepatic and renal function, and hence methotrexate should be used with extreme caution in the elderly, given the increased risk of toxicity.
- *Pregnancy*: it is teratogenic and contraindicated in pregnancy. Contraception should be used during, and for 6 months following, treatment.
- *Lactation*: breastfeeding is contraindicated.

Efficacy

- *Immunomodulation*: see relevant conditions.
- *Neuro-oncology*: within the context of PCNSL, methotrexate has been demonstrated to result in complete remission, when used as part of a regimen including cytarabine, in 46%, and a partial response was identified in a further 23%.

  With regard to the management of leptomeningeal metastases, methotrexate is the agent most commonly used for intrathecal chemotherapy. Early case series conducted in the 1980s have suggested that, in combination with whole brain radiotherapy, intrathecal methotrexate can yield a median addition survival of up to 5.7 months in patients who have demonstrated a response by 1 month.

Dosing and monitoring

Dosing

Oral doses of between 7.5mg and 25mg once per week are typically used for neuro-immune indications. The individual chapters contain further details on individual conditions.

In the context of neuro-oncology, methotrexate may be given PO, IV, or intrathecally. The dosage of methotrexate varies, depending on the BSA, clinical indication, local protocols, and other adjuvants used in the chemotherapy regimen. The exact dose for intrathecal administration depends on age, as this better correlates with CSF volume than the BSA.

Monitoring Prior to, and during, treatment monitoring includes FBC, LFTs, U&Es, urinalysis, and a clinical assessment of respiratory complications. A CXR and lung function tests should also be performed before initiation. Some clinicians advocate the unlicensed use of 5mg of oral folate on days when methotrexate is not used, to reduce side effects.

Pharmacokinetics and interactions

Pharmacokinetics

Doses of 0.1mg/kg are completely absorbed in the gastrointestinal tract, but larger doses may not be. ~50% of the drug is bound to serum proteins. The majority of the drug is excreted unchanged in the urine, with a small amount excreted in the faeces. It can be retained for several weeks in the kidneys and for several months in the liver. The serum half-life is calculated to be 2–4h following IM or oral administration of 0.06mg/kg, and this increases with increased doses.

Interactions See Table A.84.

Table A.84 Interactions of methotrexate

Medications which alter methotrexate plasma levels	Medications whose plasma levels are altered by methotrexate	Pharmacodynamic interactions
Decreased levels: acetazolamide and neomycin **Increased levels:** acitretin, ciprofloxacin, NSAIDs, nitrous oxide, penicillins, phenytoin, probenecid, proton pump inhibitors, and pyrimethamine	**Decreased levels:** digoxin **Increased levels:** theophylline	**With ciclosporin, cisplatin, doxycycline, leflunomide, sulfamethoxazole, sulfonamides, tetracycline, and trimethoprim:** there is an increased risk of toxicity **With clozapine:** there is also an increased risk of agranulocytosis

References

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Sause WT, Crowley J, Eyre HJ, *et al*. Whole brain irradiation and intrathecal methotrexate in the treatment of solid tumor leptomeningeal metastases – a Southwest Oncology Group Study. *J Neurooncol* 1988;**6**(2):107–12.

Methylphenidate

Methylphenidate has been used to treat narcolepsy since the 1950s. It is now more commonly used in the management of ADHD. It is a CNS stimulant, which is now second-line behind modafinil in the management of narcolepsy. Small studies have demonstrated its effectiveness in maintaining wakefulness; however, it is limited by its potential as a drug of abuse and well-recognized cardiovascular, cerebrovascular, and psychiatric side effects.

Uses

Licensed uses

In the USA

- *Narcolepsy*: methylphenidate is licensed for the symptomatic treatment of narcolepsy in individuals >6 years of age.

In the UK, methylphenidate is licensed for the treatment of ADHD, but not narcolepsy.

Off-licence uses

- Other sleep disorders, including cancer-related fatigue.

Presentation

- *Trade names*: Methylin®, Ritalin®, and Ritalin SR® are the only formulations licensed in the USA for use in narcolepsy. Concerta XL®, Equasym XL®, and Medikinet XL® are formulations used primarily in ADHD. Generics are available.
- *Formulations*: methylphenidate is available as a capsule, a modified (including extended/sustained)-release tablet, an oral suspension, and a standard tablet. Modified-release capsule/tablet: doses vary widely, depending on the formulation. Oral suspension: 60mL, 120mL, 150mL, and 180mL vials at a concentration of 25mg/5mL. Standard tablet: 5mg, 10mg, and 20mg.

Mechanism of action

The mechanism of action of methylphenidate in narcolepsy is not well understood. It is a CNS stimulant. Part of its action may be mediated by inhibition of dopamine and NA uptake into presynaptic neurons. This acts to stimulate the brain arousal pathways.

Toxicity and side effects

- *Common—cardiovascular*: arrhythmia, hypertension, palpitations, and tachycardia. *Dermatological*: alopecia, pruritus, rash, and urticaria. *Gastrointestinal*: abdominal pain, anorexia, diarrhoea, dry mouth, nausea, vomiting, and weight loss (potentially resulting in growth failure in children). *Musculoskeletal*: arthralgia. *Neurological*: headache is very common. Dizziness, dyskinesia, fatigue, and psychomotor hyperactivity are common. *Ophthalmological*: blurred vision. *Psychiatric*: anorexia, insomnia, and mood disorders. *Respiratory*: cough and nasopharyngitis.

- *Serious—cardiovascular*: rarely cardiac arrest and MI. *Dermatological*: anaphylaxis, angioneurotic oedema, and erythema multiforme. *Gastrointestinal*: hepatic coma has been reported. *Neurological*: cerebral arteritis, movement disorders including tics, NMS, seizures, and strokes have been reported. *Psychiatric*: mania, psychosis, and suicidality are uncommon.

Contraindications

- *Absolute*: a diagnosis or history of psychopathic/borderline personality disorder, severe mood, or psychotic disorder. Pre-existing cardio- and cerebrovascular disease, including cardiomyopathies, cerebral aneurysm or vasculitis, cerebrovascular accident, haemodynamically significant congenital heart disease, heart failure, history of MI, life-threatening arrhythmias, peripheral vascular disease, and severe hypertension. In addition, hypersensitivity to methylphenidate or its excipients, hyperthyroidism, glaucoma, and phaeochromocytoma. Methylphenidate should also not be used concomitantly or within a month of use of irreversible MAOIs.
- *Relative*: epilepsy due to lowering of the seizure threshold. Patients with pre-existing history of drug abuse and with pre-existing cardio-/cerebrovascular disease or with vascular risk factors. Pre-existing psychiatric disorders, including mood, psychotic, and tic disorders. Methylphenidate has not been studied in hepatic and renal impairment; hence caution should be used, particularly in renal impairment, due to the extensive renal metabolism of the drug.

Uses in special populations

- *Elderly*: methylphenidate has not been trialled in the elderly. The manufacturer advises against use in this population.
- *Pregnancy*: human cohort studies have suggested that first-trimester *in utero* exposure to methylphenidate does not have a significantly increased risk of major malformations. The advantages and disadvantages of ongoing use of methylphenidate in pregnancy should be discussed with the mother, and treatment decisions made on an individual basis.
- *Lactation*: methylphenidate is present in human breast milk, and case reports suggest that impaired infant growth may occur in offspring of nursing mothers on treatment; hence avoid, where possible.

Efficacy

Evidence for the use of methylphenidate in narcolepsy is limited to the results of small studies conducted in the 1980/90s. One small placebo-controlled study of 26 patients showed that treatment with methylphenidate significantly increased the patients' ability to stay awake vs placebo. A further similar study by the same group demonstrated that methylphenidate resulted in a statistically significant improvement in sleep latency, as measured by the maintenance of wakefulness test and a subjective improvement in narcolepsy symptoms.

Dosing and monitoring

Dosing

- Immediate-release tablets/solution: start treatment at 5mg bd at breakfast and lunch. This can be increased by 5–10mg at intervals of 1 week up to a maximum of 60mg, split over 2–3 doses.
- Modified-release tablets: titrate initially with immediate-release tablets, then switch to modified-release tablets (over 8h) at a later point.

Routine monitoring Prior to initiation of treatment, FBC, cardiovascular history, and vascular risk factor history should be taken. An FBC should be repeated regularly throughout treatment. BP, pulse rate, and, in children, height, weight, and appetite should be monitored 6-monthly. Patients should be regularly assessed for the emergence of psychiatric illness.

Pharmacokinetics and interactions

Pharmacokinetics

Methylphenidate is a racemic mixture of *d*- and *l*-enantiomers. The *d*-enantiomer is thought to be the active enantiomer. Bioavailability for the *d*-enantiomer is ~22%. Peak plasma concentrations occur ~1–2h post-dose. Bioavailability and peak plasma concentrations are enhanced by co-ingestion with food. Methylphenidate is 10–33% plasma-bound. The half-life is ~2h. Methylphenidate is rapidly metabolized by CES1A1, a carboxylesterase; the metabolites are believed to have little pharmacological activity. Ultimately, >95% of the metabolized drug is excreted via the renal tract, <1% as unchanged methylphenidate.

Interactions See Table A.85.

Table A.85 Interactions of methylphenidate

Medications whose plasma levels are altered by methylphenidate	Pharmacodynamic interactions
Levels increased: reports suggest methylphenidate may increase levels of coumarin anticoagulants, phenobarbital, phenytoin, primidone, SSRIs, and TCAs	**With drugs that elevate BP, e.g. halogenated anaesthetics and irreversible MAOIs:** may result in increase in BP/hypertensive crisis **With alcohol and dopaminergic drugs, e.g. DOPA and TCAs:** CNS effects may be exacerbated **With clonidine:** serious cardiovascular events, including sudden death, have been associated with this combination

References

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Methysergide

Methysergide is a semi-synthetic ergot alkaloid and was first used in 1980. It was the first prophylactic drug found to work in migraine, but its use is limited due to serious side effects, namely pulmonary and retroperitoneal fibrosis. It is also used in the treatment of cluster headache for patients who are resistant to more conventional prophylactic agents.

Uses

Licensed uses

In the UK/USA

- *Vascular headache*: methysergide is licensed for the prophylactic treatment of migraine (with or without aura), cluster headache, and other vascular headaches in patients who experience severe impairment to social and economic life, in spite of efforts to control attacks with other agents (UK), or those who suffer from one or more severe attacks a week or from extremely severe headaches (USA) in individuals aged 18 years and older.

Off-licence uses

- None.

Presentation

- *Trade names*: Sansert®, Deseril®. Generics are available.
- *Formulations*: methysergide is available as an oral tablet: 1mg (UK), 2mg (USA).

Mechanism of action

The mechanism of action for methysergide in migraine and other vascular headaches is not well understood. It has been shown to be a powerful antagonist of the $5HT_7$ and $5HT_2$ receptors, with agonist activity confirmed at the $5HT_{1B}$ receptor and possibly some agonist activity at $5HT_{1D}$. This has been shown to result in cerebral artery vasoconstriction. In addition, its role as a $5HT_2$ receptor antagonist or as an anti-inflammatory agent may also contribute to its therapeutic effects.

Toxicity and side effects

Side effects are common with methysergide, with studies showing that 20–45% of patients experience adverse effects. The majority are related to vasoconstriction. 10% discontinue the drug, due to toxicity. The most worrisome side effect is that of fibrosis, which affects 1 in 5000 patients. It may regress on stopping the drug, but, with retroperitoneal fibrosis, renal function may remain impaired after withdrawal.

- *Common—cardiovascular*: dizziness, peripheral oedema, peripheral vascular disease. *Endocrine*: weight gain. *Gastrointestinal*: diarrhoea, epigastric pain, nausea, vomiting. *Psychiatric*: anxiety, depression, euphoria, feelings of uneasiness/unreality.
- *Serious—cardiovascular*: angina, cardiac valve fibrosis, MI. *Gastrointestinal*: retroperitoneal fibrosis. *Neurological*: stroke. *Respiratory*: pulmonary fibrosis.

Contraindications

- *Absolute*: methysergide is contraindicated in collagen disorders, fibrotic disease, heart valve disorders, ischaemic heart disease, lung disease, malnutrition, peptic ulcer disease, peripheral vascular disease, pregnancy, severe infection, thrombophlebitis, leg cellulitis, and uncontrolled hypertension. It is contraindicated in liver and renal impairment.

Uses in special populations

- *Elderly*: there are no studies looking specifically at methysergide use in the elderly. Given that the elderly are more likely to have a contraindication to methysergide use (cardiovascular disease, renal impairment), it should be used with caution.
- *Pregnancy*: methysergide is contraindicated in pregnancy, as it may initiate labour.
- *Lactation*: no studies have looked at methysergide and its concentration in breast milk. However, ergot alkaloids are known to be excreted in breast milk and cause gastrointestinal disturbance in the infant. Hence methysergide should not be used in nursing mothers.

Efficacy

There have been several RCTs comparing methysergide with placebo and other drugs used in migraine prophylaxis. The dose of methysergide used has been variable, ranging between 3mg to 6 mg daily. All but one of the studies found that methysergide was superior to placebo in reducing the frequency of attacks. It was comparable to pizotifen and propranolol in reducing attack frequency and severity of headache. Methysergide was associated with a high rate of adverse events. There are only observational study data for the use of methysergide in cluster headache. These studies have found that methysergide is effective in preventing attacks in some patients with chronic and episodic cluster headaches. The percentage of patients reporting improvement ranges from 20% to 73%.

Dosing and monitoring

Dosing

Start treatment at 1mg od. The dose can be titrated to 2mg qds for the prevention of migraine and cluster headache over a couple of weeks (normal maintenance dose 2–8mg in divided doses), with close monitoring for side effects. If no effect is seen after 3 weeks, it should be stopped. Methysergide should not be used for >6 months and, when stopped, should be weaned over a week to prevent rebound headache. It can be restarted after a 1–2 months' drug holiday.

Routine monitoring

Patients should be assessed for signs of fibrosis, including symptoms of backache, urinary symptoms, and leg pain. Clinical examination, including auscultation for murmurs and assessing peripheral pulses, should be done on every visit. The MHRA (UK) advocate ongoing 6 monthly screening for fibrosis with echo, abdominal MRI, and pulmonary function tests whilst on treatment.

Pharmacokinetics and interactions

Pharmacokinetics

Methysergide is rapidly and well absorbed from the gut. Peak plasma concentrations are reached in 1h from ingestion. Concomitant food ingestion does not affect absorption or bioavailability. It undergoes extensive first-pass metabolism in the liver by the cytochrome P450 enzyme: CYP3A4 to the active metabolite methylergometrine. The oral bioavailability of methysergide is ~13%. About 66% of the drug is protein-bound. Both methysergide and methylergometrine are excreted by the kidney. The excretion of methysergide is biphasic, due to its conversion to methylergometrine which has a longer half-life than its parent drug; the half-life is 2.7h for the first phase, and 10h for the second phase.

Interactions See Table A.86.

Table A.86 Interactions of methysergide

Medications which alter methysergide plasma levels	Pharmacodynamic interactions
Levels increased: CYP3A inhibitors, e.g. azole antifungals, cimetidine, macrolide antibiotics, protease inhibitors, quinupristin/dalfopristin	**With β-blockers:** increased risk of vasoconstriction and hypertension **With triptans:** these should not be given within 24h of methysergide, due to increased risk of vasospasm

References

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Mexiletine

Mexiletine is a sodium channel blocker, initially used as an antiarrythmic agent. Since 1983, it has been used off-licence in the treatment of myotonia. It has recently received orphan designation in both the European Union (EU) and USA, which has stimulated research in this area.

Uses

Licensed uses

In the UK/USA
(Licensing is the same.)
- Mexiletene has no licensed neurological uses.

Off-licence uses
- Treatment of myotonia in DM1 and non-dystrophic myotonias.

Presentation

- *Trade name*: Mexitil®, Novo-Mexiletine®. Generics are available.
- *Formulation*: oral capsules of 150mg, 200mg, and 250mg

Mechanism of action

Mexiletine is a Vaughan–Williams class Ib antiarrhythmic that targets voltage-gated sodium channels. The non-dystrophic myotonias are characterized by delayed skeletal muscle relaxation. They are caused by mutations in either chloride channel (*CLCN1*) or sodium channel (*SCN4A*) genes. This results in an overactive ion channel and prolonged depolarization of the muscle fibre membrane. Mexiletine blocks the sodium channel, thereby reducing muscle fibre excitability.

Toxicity and side effects

- *Common—cardiovascular*: bradycardia, chest pain, hypotension, prolongation of PR/QTc intervals/QRS duration, palpitations, syncope. *Gastrointestinal*: dyspepsia, nausea, vomiting. *Neurological*: coordination difficulties, light-headedness, tremor.
- *Serious—cardiovascular*: AV block, cardiogenic shock.

Contraindications

- *Absolute*: second- and third-degree heart block, cardiogenic shock, QTc prolongation.
- *Relative*: in renal failure with CrCl <10mL/min, 50–75% of the normal dose should be given. In hepatic impairment, the half-life is doubled, and the dose should be reduced by 25–30%.

Uses in special populations

- *Elderly*: the elderly experience an age-related reduction in hepatic and renal function and are more prone to cardiovascular disease, and hence dose reduction is often required.
- *Pregnancy*: animal studies have not demonstrated fetal teratogenicity. There are no controlled studies in humans. The manufacturer advises caution in pregnancy and use only if benefit exceeds risks.
- *Lactation*: mexiletine is found in breast milk at similar concentrations to plasma; hence breastfeeding should be avoided.

Efficacy

Two small randomized trials have demonstrated efficacy of mexiletine for myotonia in patients with DM1. In one, 150mg tds mexiletine reduced grip relaxation time from 2.55s with placebo to 1.32s. Similar results were obtained for 200mg tds mexiletine. Two randomized trials have shown that 200mg tds mexiletine is an effective, safe, and well-tolerated treatment for myotonia-induced stiffness and pain in non-dystrophic myotonia. A short course (4–7 weeks) of mexiletine reduced handgrip myotonia by an average of 0.33s and improved patient-reported quality of life scores by 2.7 points, both of which were statistically significant.

Dosing and monitoring

Dosing

Typical dose for myotonia is 150–200mg tds.

Monitoring Cardiology evaluation for risk assessment should be considered prior to initiation, including a baseline ECG and QTc interval monitoring. Regular ECGs should be performed, due to the proarrhythmogenic nature of mexiletine.

Pharmacokinetics and interactions

Pharmacokinetics

Mexiletine has a bioavailability of 80–95%. Onset of action is 30–120min, with peak plasma levels reached at 2–3h. It is 50–60% protein-bound. The half-life is 10–14h, longer in hepatic or cardiac failure. Metabolism is hepatic by CYP2D6 (and, to a lesser extent, CYP1A2), to largely inactive metabolites. Excretion is urinary (10–15% as unchanged drug).

Interactions See Table A.87.

Table A.87 Interactions of mexiletine

Medications which alter mexiletine plasma levels	Medications whose plasma levels are altered by mexiletine
Levels decreased: cimetidine, cyproterone, etravirine, fosphenytoin, phenytoin, vemurafenib **Levels increased:** cimetidine, darunavir, deferasirox, peginterferon α-2b, SSRIs	**Levels increased:** bendamustine, clozapine, pirfenidone, pomalidomide, theophylline

Midodrine

Midodrine was first used in the 1980s for the treatment of dysautonomia and orthostatic hypotension. It can be used in PD and other disorders associated with autonomic neuropathy for the management of orthostatic hypotension when conservative measures have failed.

Uses

Licensed uses

In the USA/UK

- *Orthostatic hypotension*: midodrine is licensed for the treatment of symptomatic orthostatic hypotension, due to autonomic dysfunction, in patients not responding to standard clinical care in individuals aged 18 years and older.

Off-licence uses

- None.

Presentation

- *Trade names*: Amatine®, Apo-Midodrine®, Bramox®, ProAmatine®, and Gutron®. Generics are available.
- *Formulations*: tablets: 2.5mg, 5mg, and 10mg.

Mechanism of action

Midodrine is a prodrug with an active metabolite desglymidodrine which is a peripherally acting α1-adrenoceptor agonist. It increases the BP via vasoconstriction. Midodrine does not cross the blood–brain barrier and does not stimulate β-adrenergic receptors, and hence does not increase the heart rate.

Toxicity and side effects

- *Common—cardiovascular*: supine hypertension (BP above or equal to 180/110mmHg) with daily doses above 30mg (less commonly seen at lower doses). *Dermatological*: flushing, piloerection, pruritus (mainly of the scalp), and rash. *Gastrointestinal:* dyspepsia, nausea, stomatitis, and vomiting. *Neurological*: paraesthesiae. *Ophthalmological*: increased tear production. *Renal*: dysuria, urinary retention, and urgency.
- *Serious—cardiovascular*: chest pain. *Neurological*: stroke.

Contraindications

- *Absolute*: hypersensitivity to midodrine or its excipients, severe organic heart disease, acute renal failure, urinary retention, phaeochromocytoma, thyrotoxicosis, persistent and significant supine hypertension.
- *Relative*: patients with a history of urinary retention, diabetes, and, glaucoma. Reduce the dose in renal impairment (2.5mg tds, and gradually increase as tolerated). Caution should be taken in renal impairment, although no dose alteration is routinely recommended.

Uses in special populations

- *Elderly*: no dose alteration is routinely required. The elderly experience an age-related decline in their renal function and are also more prone to hypertensive, cardiovascular, and cerebrovascular side effects, and hence midodrine should be used with caution in this group.
- *Pregnancy*: animal studies showed adverse events. Avoid in pregnancy, unless the possible clinical benefits clearly outweigh the potential hazards.
- *Lactation*: excretion in breast milk is not known. Use with caution in nursing mothers.

Efficacy

There is a lack of evidence for the use of midodrine specifically in PD-associated orthostatic hypotension. For this reason, it has been labelled as an investigational treatment in a recent MDS review. However, several trials have assessed its use in various causes of neurogenic hypotension where it was found to be efficacious, safe, and tolerable. A 6-week, randomized, double-blind multicentre study (n = 171) assessed midodrine (10mg tds) against placebo for neurogenic hypotension. The primary endpoints were improvement in standing systolic BP, symptoms of light-headedness, and global symptom relief score. Midodrine resulted in significant improvements in standing systolic BP (p <0.001), reported symptoms by the second week (p = 0.001), and global symptom relief score (p = 0.03). The main adverse effects were pilomotor reactions, urinary retention, and supine hypertension.

It can be used alone or in combination with fludrocortisone.

Dosing and monitoring

Dosing

Start treatment at 2.5mg bd to tds, increasing gradually up to 10mg tds. Supine hypertension is common (25%). The last dose should be taken at least 4h before sleep. Some patients' orthostatic hypotension may worsen following commencement of midodrine.

Routine monitoring Regularly monitor the BP and renal function.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is 93%. Absorption is not affected by food. Midodrine is a prodrug and is rapidly metabolized by deglycination, both hepatically and by other tissues, to desglymidodrine. The T_{max} of midodrine and desglymidodrine is 30min and 1–2h, respectively. The half-lives of midodrine and desglymidodrine are 30min and 1–2h, respectively. Elimination is predominantly by renal secretion as desglymidodrine.

Interactions See Table A.88.

Table A.88 Interactions of midodrine

Pharmacodynamic interactions
With β-blockers, calcium channel blockers, and cardiac glycosides: may enhance their bradycardic effect
With other vasopressors, e.g. phenylephrine: may increase their pressor effects

Reference

Low PA, Gilden JL, Freeman R, Sheng KN, McElligott MA. Efficacy of midodrine vs placebo in neurogenic orthostatic hypotension: a randomized, double-blind multicenter study. *JAMA* 1997;**277**(13):1046–51.

Mirabegron

Mirabegron was first licensed for use in 2013 in the UK for the management of OAB. It acts via the β3-adrenoceptor, in contrast to the other main group of drugs used for this indication—the anticholinergics which act via muscarinic receptors. It is an effective drug, which is often used where anticholinergics have failed due to lack of efficacy or poor tolerability, e.g. due to dry mouth.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- Mirabegron is licensed for the symptomatic management of OAB syndrome in individuals aged 18 years and older.
- In the UK, NICE recommends its use as a second-line agent if patients are intolerant to, or treatment is ineffective with, anticholinergics.

Off-licence uses

- None.

Presentation

- *Trade names*: Betmiga® and Myrbetriq®. Generics are not available.
- *Formulations*: mirabegron is available as an oral tablet in 25mg and 50mg doses.

Mechanism of action

Mirabegron is a β3-adrenoceptor agonist. At commonly used doses, it is highly selective for β3 receptors, when compared to β1 and β2 adrenoceptors. It acts during the urine storage phase by promoting detrusor muscle relaxation and increasing the volume of urine that can be stored prior to voiding.

Toxicity and side effects

- *Common—cardiovascular*: hypertension and tachycardia. *Urology*: UTI.
- *Serious—cardiovascular*: AF. *Dermatological*: leukocytoclastic purpura.

Contraindications

- *Absolute*: hypersensitivity to mirabegron or its excipients, and severe hypertension.
- *Relative*: patients with congenital or acquired long QT syndrome and patients with urinary retention. Avoid if eGFR <15mL/min/1.73m^2 (as there is no available information with regard to use) and if there is concomitant use of strong CYP450 inhibitors and eGFR <30mL/min/1.73m^2. Reduce the dose to 25mg od if eGFR 15–30mL/min/1.73m^2 or if there is concomitant use of strong CYP450 inhibitors and eGFR 30–89mL/min/1.73m^2. Avoid in severe hepatic impairment (as there is no available information with regard to use), and avoid in moderate hepatic impairment if there is concomitant use of strong CYP450 inhibitors. Reduce the dose to 25mg od in moderate hepatic impairment, and in mild hepatic impairment if there is concomitant use of strong CYP450 inhibitors.

Uses in special populations

- *Elderly*: no dose adjustments are required in the elderly population.
- *Pregnancy*: studies in animals have suggested reproductive toxicity. There have been no controlled studies in humans; hence mirabegron should not be used in pregnancy, and effective contraception should be used in all women of childbearing age while on treatment.
- *Lactation*: mirabegron is present in mammalian milk; its potential effects on the newborn are unclear, and hence breastfeeding should be avoided while on treatment.

Efficacy

Pooled analysis of the first three RCTs to assess the effects of mirabegron on urgency and incontinence in adult patients with OAB showed that, compared to placebo, there was a significant reduction in the number of incontinence and micturition episodes over 24h; 0.4 fewer episodes of incontinence, compared to placebo (p <0.001, mean baseline episodes 2.73, mean change with mirabegron −1.49 vs −1.1 with placebo); and 0.55 fewer episodes of micturition, compared to placebo (p <0.001, mean baseline episodes 11.58, mean change with mirabegron −1.75 vs −1.2 with placebo). RCTs have compared mirabegron to tolterodine tartrate MR, with several trials suggesting that mirabegron may be the more effective agent; however, a NICE technology appraisal conducted a Bayesian analysis of mirabegron compared to various anticholinergics and concluded that there was no significant difference between these agents in terms of their effects on urgency and incontinence.

Dosing and monitoring

Dosing

Patients should be started and maintained on the effective dose of 50mg od, with no adjustment routinely required, unless there is renal or hepatic impairment (see Contraindications above).

Routine monitoring BP should be measured at baseline and then regularly during treatment.

Pharmacokinetics and interactions

Pharmacokinetics

Mirabegron has a bioavailability of 29%. T_{max} is 3–4h. Food increases bioavailability and reduces the time taken post-dose at which T_{max} is reached. Steady-state plasma concentrations are reached at 1 week. Mirabegron is extensively protein-bound (71%). Mirabegron is metabolized by multiple pathways, including the CYP450 enzyme system, although *in vitro* studies suggest there is unlikely to be autoinduction or inhibition of these enzymes. The terminal elimination half-life is ~50h. 55% of mirabegron is excreted in urine (45% of this as unchanged drug) and the rest in faeces.

Interactions See Table A.89.

Table A.89 Interactions of mirabegron

Medications which alter plasma levels of mirabegron	Medications whose plasma levels are altered by mirabegron	Pharmacodynamic interactions
Levels increased: CYP3A inhibitors, e.g. clarithromycin and ketoconazole **Levels decreased:** CYP3A inducers, e.g. rifampicin, may reduce plasma levels	**Levels increased:** digoxin	**With anticholinergics:** increased risk of urinary retention **With drugs which prolong the QT interval:** increased risk of ventricular arrhythmia

References

National Institute for Health and Care Excellence (2013). *Mirabegron for treating symptoms of overactive bladder*. NICE technology appraisal TA290. Available at: https://www.nice.org.uk/guidance/ta290.

Nitti VW, Khullar V, Van Kerrebroeck P, *et al*. Mirabegron for the treatment of overactive bladder: a prespecified pooled efficacy analysis and pooled safety analysis of three randomised, double-blind, placebo-controlled, phase III studies. *Int J Clin Pract* 2013;**67**(7):619–32.

Mitoxantrone

Mitoxantrone was first used as a chemotherapeutic agent in the 1970s and continues to be used to treat a range of malignancies. It was shown to be effective in relapsing forms of MS in 1997 and is used as second-line treatment, given the risk of cardiotoxicity and leukaemia.

Uses

Licensed uses

In the USA

- *RRMS, SPMS, and progressive–relapsing MS (PRMS)*: mitoxantrone is licensed to reduce disability and frequency of clinical relapses in patients with worsening RRMS, SPMS, or PRMS.

It is not licensed in the UK for use in MS.

Presentation

- *Trade name*: Novantrone® and Onkotrone®. Generics are available.
- *Formulation*: vial of 2mg/mL concentrate for IV infusion: 10mL, 12.5mL, and 15mL.

Mechanism of action

Mitoxantrone is a topoisomerase II inhibitor that prevents DNA synthesis and repair. It inhibits B cell and T cell proliferation and function, and reduces the release of pro-inflammatory cytokines, including IFN-γ.

Toxicity and side effects

- *Common—dermatological*: blue discoloration of nails/skin and rash. *Gastrointestinal*: deranged LFTs, dysgeusia, nausea, and vomiting. *Genitourinary*: blue-green discoloration of urine. *Gynaecological*: amenorrhoea. *Immunological*: fever. *Psychiatric*: anxiety.
- *Serious—cardiovascular*: cardiomyopathy and congestive cardiac failure. *Dermatological*: extravasation causing erythema/necrosis. *Haematological*: acute myeloid leukaemia (0.3% of patients, 80% of whom were exposed to a dose >60mg/m^2), anaemia, leucopenia, and thrombocytopenia. *Immunological*: hypersensitivity.

Contraindications

- *Absolute*: hypersensitivity to mitoxantrone and other anthracyclines.
- *Relative*: bone marrow suppression. The effect of the drug on patients with hepatic and renal impairment has not been studied, and caution with careful monitoring is advised.

Use in special populations

- *Elderly*: mitoxantrone has not been studied in the elderly, and caution is advised.
- *Pregnancy*: this drug is contraindicated in pregnancy, due to potential teratogenicity. Contraception should be used during, and for 6 months following, treatment.
- *Lactation*: breastfeeding is contraindicated.

Efficacy

The Mitoxantrone in MS (MIMS) study compared treatment with mitoxantrone at a dose of 12mg/m^2 every 3 months with placebo. It showed a 60% reduction in number of relapses per subject in the treatment group over 2 years.

Dosing and monitoring

Dosing

There are two commonly used regimens for mitoxantrone in MS: 12mg/m^2 every 3 months for 2 years (MIMS protocol) or 20mg administered with 1g of IV methylprednisolone every 4 weeks for 6 months (French–British protocol).

Routine monitoring Prior to treatment initiation, FBC, pregnancy test, cardiac examination, ECG, and echocardiography or multigated acquisition (MUGA) scan are performed. Regular FBC monitoring should be continued during treatment, and annual echocardiography should be continued indefinitely to measure for signs of cardiotoxicity. Patients should not receive a lifetime cumulative dose >140mg/m^2 to minimize cardiotoxicity.

Pharmacokinetics and interactions

Pharmacokinetics

Mitoxantrone is given as an IV infusion. 25% of the active drug is metabolized to an inactive form and conjugated in the hepatobiliary system where it is excreted. 65% of unchanged drug is excreted in the urine. Mitoxantrone is excreted via the hepatobiliary and renal systems, with a variable terminal half-life of ~4 days.

Interactions See Table A.90.

Table A.90 Interactions of mitoxantrone

Medications which alter mitoxantrone plasma levels	Pharmacodynamic interactions
Increased levels: ciclosporin	**With clozapine:** there is an increased risk of agranulocytosis

References

Edan G, Miller D, Clanet M, *et al*. Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomized multicenter study of active disease using MRI and clinical criteria. *J Neurol Neurosurg Psychiatry* 1997;**62**(2):112–18.

Hartung HP, Gonsette R, König N, *et al*.; Mitoxantrone in Multiple Sclerosis Study Group (MIMS). Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet* 2002;**360**(9350):2018–25.

Millefiorini E, Gasperini C, Pozzilli C, *et al*. Randomised placebo-controlled trial of mitoxantrone in relapsing-remitting multiple sclerosis: 24-month clinical and MRI outcome. *J Neurol* 1997;**244**(3):153–9.

Modafinil

Modafinil was first marketed in the UK in 2002. It is primarily used in the treatment of excessive daytime sleepiness in narcolepsy, although it is often used off-licence as a supposed cognitive enhancer and in a range of fatigue-related conditions. Its advantages include od dosing and a relatively benign side effect profile, although caution is advised when used in patients with a cardiovascular or psychiatric history.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- *Narcolepsy*: modafinil is licensed for the treatment of excessive sleepiness in the management of narcolepsy, with or without cataplexy, in individuals >18 years of age.

In the USA

- *Shift work sleep disorder/obstructive sleep apnoea/hypopnoea syndrome*: modafinil is licensed for the treatment of excessive sleepiness in these conditions in individuals >18 years of age.

Off-licence uses

- Treatment of fatigue in MS and PD.

Presentation

- *Trade names*: Provigil®. Generics are available.
- *Formulations*: modafinil is available as a tablet in doses of 100mg and 200mg.

Mechanism of action

The precise mechanism of action of modafinil is unclear. Studies have demonstrated its use results in a marked wake-promoting action, without an effect on the occurrence of cataplexy. It has been shown to block dopamine and, to a lesser extent, NA reuptake by binding to dopamine and NA transporters. Part of its action may also be mediated by elevating hypothalamic histamine levels. It is relatively selective in its actions, with negligible interactions at other receptors involved in the sleep–wake process.

Toxicity and side effects

- *Common—cardiovascular*: palpitations, chest pain, tachycardia, and vasodilatation. *Gastrointestinal*: abdominal pain, abnormal LFTs, anorexia, constipation, diarrhoea, dry mouth, dyspepsia, and nausea. *Neurological*: headache is very common (>20%) and dose-dependent, and normally resolves within a few days. Dizziness, fatigue, and paraesthesiae are common. *Ophthalmological*: blurred vision. *Psychiatric*: confusion, insomnia, and mood disorders.

- *Serious—cardiovascular*: arrhythmia. *Dermatological*: angio-oedema, drug rash with eosinophilia and systemic symptoms, Stevens–Johnson syndrome, and toxic epidermal necrolysis are very rare but have been reported. *Immunological*: multiorgan hypersensitivity reaction has been reported. *Psychiatric*: mania, psychosis, and suicidal ideation have been reported.

Contraindications

- *Absolute*: cardiac arrhythmias, history of cor pulmonale, left ventricular hypertrophy, or CNS stimulant-induced mitral valve prolapse, hypersensitivity to modafinil or its excipients, and uncontrolled hypertension.
- *Relative*: presence or history of alcohol or drug abuse, hypertension, mood disorders, and psychosis. The modafinil dose should be halved in severe hepatic impairment. Limited information is available with regard to use in renal impairment—modafinil should be used with caution.

Uses in special populations

- *Elderly*: the manufacturer advises using half of the usual starting dose in this population. The elderly are also more likely to have cardiovascular co-morbidity and are more prone to cardiac side effects.
- *Pregnancy*: animal studies show an increased incidence of early embryo/fetal loss, stillbirth, and an increased incidence of skeletal variations in surviving offspring. There have been no trials in humans. The manufacturer advises against use in pregnancy and recommends women of childbearing age to take appropriate contraception (oestrogen levels in oestrogen-containing contraceptives are reduced, hence alternative contraceptives are required).
- *Lactation*: animal studies have demonstrated modafinil secretion in mammalian milk. Human studies have not been performed. The manufacturer advises against use in nursing women.

Efficacy

A recent meta-analysis, published in 2010, involving 1054 patients demonstrated that modafinil vs placebo improved scores on the Epworth Sleepiness Scale by a WMD of −2.73 (95% CI −3.39 to −2.08). Improvement in the maintenance of wakefulness test vs placebo was by a WMD of 2.82min (95% CI 2.4–3.24). No difference was identified in the incidence of cataplexy between modafinil and placebo groups. A further long-term multicentre RCT published in 2010 demonstrated, through serial quality of life scores, that the efficacy of modafinil was maintained, without evidence of tolerance, throughout 40 weeks of treatment.

Dosing and monitoring

Dosing

Start treatment at 200mg daily in 1–2 divided doses. If administered as one dose, give in the morning; if as two doses, administer the second at noon. This can be increased by 100mg increments to a maximum of 400mg, although the evidence is inconsistent as to whether high doses improve clinical outcomes.

Routine monitoring BP and an ECG should be recorded at baseline. BP and heart rate should be monitored frequently throughout therapy, and treatment should be discontinued if arrhythmias, chest pain, or uncontrolled hypertension arises.

Pharmacokinetics and interactions

Pharmacokinetics

Modafinil is a racemic mixture of *d*- and *l*-enantiomers. These enantiomers are similar with respect to their pharmacological activity but differ in that the *l*-enantiomer has a three times longer half-life than the *d*-enantiomer. The bioavailability of modafinil is unknown. Peak plasma levels occur 2–4h post-dose. Food co-ingestion does not affect bioavailability; however, it does delay peak plasma levels by 1h. Steady state is reached after 2–4 days. Modafinil is ~60% bound to plasma proteins. Modafinil is primarily eliminated by hepatic metabolism, including hydrolytic deamidation, S-oxidation, etc. The metabolites are pharmacologically inactive. Modafinil may cause weak induction of CYP3A4/5 activity, but the effect is felt to be clinically insignificant. Modafinil is ultimately eliminated by the renal tract, <10% as unchanged modafinil.

Interactions See Table A.91.

Table A.91 Interactions of modafinil

Medications which alter modafinil plasma levels	Medications whose plasma levels are altered by modafinil
Levels decreased: inducers of cytochrome P450 activity, e.g. carbamazepine and phenobarbital	**Levels decreased:** oestrogen component of contraceptives. *In vitro* testing has suggested modafinil may induce CYP3A enzymes, resulting in a reduction in drugs metabolized by this pathway, including ciclosporin, HIV protease inhibitors, and midazolam
	Levels increased: due to possible suppression of CYP2C19 and CYP2C9, the following drug levels may rise: diazepam, omeprazole, phenytoin, propranolol, SSRIs, TCAs, and warfarin

References

Broughton RJ, Fleming JA, George CF, *et al*. Randomized, double-blind, placebo controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness. *Neurology* 1997;**49**(2):444–51.

Golicki D, Bala MM, Niewada M, *et al*. Modafinil for narcolepsy: systematic review and meta-analysis. *Med Sci Monit* 2010;**16**(8):RA177–86.

Mitler MM, Harsh J, Hirshkowitz M, *et al*. Long-term efficacy and safety of modafinil (PROVIGIL®) for the treatment of excessive daytime sleepiness associated with narcolepsy. *Sleep Med* 2000;**1**(3):231–43.

Mycophenolate mofetil

Mycophenolate mofetil was developed in the 1990s as an immunosuppressant for transplantation. It has since been used in several autoimmune neurological diseases.

Uses

Licensed uses

In the UK/USA

There are no licensed neurological uses.

Off-licence uses—amongst others include:

- MG (second-line, chronic).
- NMO (second-line).
- PM.
- DM.

Presentation

- *Trade names*: Arzip®, CellCept®, Myfenax®, and Myfortic®. Generics are available.
- *Formulations*: mycophenolate is available as an oral capsule, (CellCept®), an oral suspension (CellCept®), an oral tablet (Arzip®, CellCept®, Myfenax®, and Myfortic®), and a powder for IV infusion (CellCept®). Oral capsule: 250mg. Oral suspension (1g/5mL): 175mL. Oral tablet: 180mg, 360mg, and 500mg. Powder for infusion: 500mg vial.

Mechanism of action

Mycophenolate mofetil is a reversible inhibitor of inosine monophosphate dehydrogenase, an enzyme used in guanosine nucleotide synthesis. The drug inhibits B and T lymphocyte proliferation by preventing DNA synthesis.

Toxicity and side effects

- *Common—cardiovascular*: hyper-/hypotension and tachycardia. *Dermatological*: acne, alopecia, and fungal skin infections. *Endocrine*: hypercholesterolaemia, hyperglycaemia, hyper-/hypokalaemia, hyperuricaemia, hypocalcaemia, hypomagnesaemia, and hypophosphataemia. *Gastrointestinal*: constipation, dyspepsia, flatulence, gastroenteritis, gingival hyperplasia, ileus, and stomatitis. *Genitourinary*: UTI. *Gynaecological*: candidiasis. *Haematological*: anaemia, leucocytosis/leucopenia, and thrombocytopenia. *Musculoskeletal*: arthralgia. *Neurological*: dizziness, headache, hypertonia, myasthenic syndrome, paraesthesiae, seizure, somnolence, and tremor. *Psychiatric*: agitation, anxiety, confusion, depression, and insomnia. *Respiratory*: cough, dyspnoea, pleural effusions, and respiratory tract infections.
- *Serious—dermatological*: skin cancer. *Endocrine*: acidosis and hyper-/hypokalaemia. *Gastrointestinal*: colitis, gastrointestinal ulceration/bleeding, hepatic impairment, pancreatitis, and peritonitis. *Genitourinary*: acute kidney injury. *Haematological*: Leucopaenia and pure red cell aplasia. *Immunological*: hypersensitivity and increased risk of infections and malignancies. *Neurological*: seizures. Progressive multifocal leucoencephalopathy has been reported. *Respiratory*: interstitial lung disease.

Contraindications

- *Absolute*: hypersensitivity to mycophenolate.
- *Relative*: dose reductions may be required in patients with severe renal impairment but are not required in those with hepatic impairment.

Use in special populations

- *Elderly*: the elderly experience an age-related decline in renal function, and hence renal function should be monitored. In general, similar dosing to the usual adult doses can be used in the elderly.
- *Pregnancy*: mycophenolate is contraindicated in pregnancy, and contraception should be used during, and for 6 weeks following, therapy.
- *Lactation*: breastfeeding should be avoided, given the drug is present in breast milk.

Efficacy

See relevant conditions in Chapter 6, Inflammatory disorders of the central nervous system.

Dosing and monitoring

Dosing

An oral dose of 0.25–1.5g bd can be used. See individual conditions in Chapter 6, Inflammatory disorders of the central nervous system for further information.

Monitoring FBC needs to be assessed prior to initiation, and then weekly during the first month, twice-monthly in the second and third months, and monthly thereafter to monitor for neutropenia. A pregnancy test is also required prior to initiation. Chickenpox can be fatal in the immunocompromised, and patients should be advised to seek medical help if they are not immune and become exposed.

Pharmacokinetics and interactions

Pharmacokinetics

Mycophenolate mofetil has an oral bioavailability of 94%. It undergoes complete pre-systemic metabolism to its active metabolite mycophenolic acid (MPA) by hydrolysis in the gastrointestinal tract and liver. Time to peak plasma concentration varies between formulations, but it is typically 1–3h. Secondary peaks in serum concentrations occur after 6h following enterohepatic recirculation. MPA is 97% bound to plasma albumin. MPA is further metabolized to an inactive form by glucuronyl transferase. Of an administered dose, 93% is excreted into the urine, with 6% in the faeces.

Interactions See Table A.92.

Table A.92 Interactions of mycophenolate mofetil

Medications which alter mycophenolate plasma levels	Medications whose plasma levels are altered by mycophenolate	Pharmacodynamic interactions
Decreased levels: antacids, co-amoxiclav, colestyramine, iron supplements, metronidazole, norfloxacin, rifampicin, and sevelamer **Increased levels:** aciclovir and ganciclovir	**Increased levels:** aciclovir and ganciclovir	Vaccinations may be less effective, and live vaccinations should be avoided

Natalizumab

This monoclonal antibody was introduced as a disease-modifying agent in 2004. It is markedly effective at reducing the relapse rate in MS, but longterm use in JC positive patients is associated with the risk of developing life-threatening PML. But can rarely be associated with potentially fatal PML.

Uses

Licensed uses

In the UK

- *Highly active RRMS*: natalizumab is indicated as a single DMT for those with '*rapidly evolving severe*' RRMS and those with '*high disease activity despite treatment*'.
  - *Rapidly evolving severe RRMS* is defined as two or more disabling relapses in 1 year, with at least one gadolinium-enhancing lesion on brain MRI or a significant increase in T2 lesion load.
  - *High disease activity despite treatment* is defined as either having at least one relapse in the previous year on IFN-β or glatiramer acetate with at least nine T2 hyperintense lesions on brain MRI or having one gadolinium-enhancing lesion. This includes patients with unchanged/increased relapse rates or ongoing severe relapses, as compared to the previous year.

In the USA

- *MS*: natalizumab is licensed for relapsing forms of MS.

Presentation

- *Trade name*: Tysabri®. Generics are not available.
- *Formulation*: vial of 20mg/mL concentrate for IV infusion: 15mL.

Mechanism of action

Natalizumab is a recombinant humanized anti-α_4-integrin antibody. It prevents the migration of leucocytes across the blood–brain barrier to sites of CNS inflammation. It binds to the $\alpha_4\beta_1$-integrin molecule present on the surface of lymphocytes. This inhibits binding of integrin to the vascular cell adhesion molecule 1 (VCAM-1) endothelial receptor that mediates the migration of leucocytes into the brain parenchyma.

Toxicity and side effects

- *Common—dermatological*: urticaria. *Gastrointestinal*: nausea and vomiting. *Genitourinary*: UTI. *Immunological*: fever and rigors. *Musculoskeletal*: arthralgia. *Neurological*: dizziness, fatigue, and headache. *Respiratory*: nasopharyngitis.
- *Serious—gastrointestinal*: hepatic impairment. *Immunological*: anaphylaxis, immune reconstitution inflammatory syndrome (IRIS) on drug withdrawal, and opportunistic infections. *Neurological*: PML (see Progressive multifocal leukoencephalopathy, p. 542).

Contraindications

- *Absolute*: hypersensitivity, PML, pre-existing immunosuppression, concurrent IFN-β or glatiramer acetate treatment, and active malignancy (excluding basal cell carcinoma).

- *Relative*: the effect of the drug on patients with hepatic and renal impairment has not been studied, but liver function can be exacerbated with this drug. Regular LFT monitoring in patients with hepatic impairment is advised, but initial dose adjustment is not necessary.

Use in special populations

- *Elderly*: natalizumab has not been studied in the elderly.
- *Pregnancy*: studies in animals have demonstrated teratogenicity, but the potential risk in humans is unknown. Active contraception should be used during, and for 3 months after, treatment.
- *Lactation*: breastfeeding should be avoided.

Efficacy

The *AFFIRM* trial demonstrated a 68% reduction in the ARR at 1 year, compared to placebo, and a 42% reduction in sustained disability accumulation over 2 years, compared to placebo. MRI measures of disease activity were very significantly reduced by natalizumab, which produced a 92% decrease in gadolinium-enhancing lesions (means 2.4 vs 0.2; $p < 0.001$), 83% decrease in new or enlarging T2 lesions (means 11 vs 1.9; $p < 0.001$), and 76% decrease in new T1 hypointense lesions (means 4.6 vs 1.1; $p < 0.001$), compared with placebo, over 2 years. Brain atrophy was greater in year 1 but significantly less in year 2, compared with the placebo group.

The *SENTINEL* study compared treatment with a combination of natalizumab and SC IFN-β1a with IFN-β1a alone and found significant benefits of combination treatment in terms of ARR and disability accumulation, but this was associated with an unacceptable increase in side effects, including two cases of PML. The ongoing Tysabri Observational Program (TOP) has to date shown that 56% of treated patients remain free of clinical disease activity after 30 months and that the EDSS, a disability score commonly used in MS, remains stable after 4 years.

Dosing and monitoring

Dosing

This drug is administered as a 300mg IV infusion lasting an hour every 4 weeks. Treatment is generally started once the patient has stopped taking IFN-β or glatiramer for 4–6 weeks. Other immunosuppressants may require different washout periods.

Routine monitoring FBC, and liver and renal function are monitored every 4 weeks. Patients must be observed and monitored for signs of hypersensitivity during, and for 1h following, the first infusion, and then during subsequent infusions. A course of corticosteroids on treatment withdrawal should be considered to minimize the severity of IRIS, which is very common and occurs within 3 months of cessation of natalizumab. Antibodies against natalizumab can develop following treatment. These antibodies predispose to hypersensitivity reactions and decrease efficacy. Assays are commercially available and are recommended in the event of poor response to treatment or prominent infusion reactions.

Progressive multifocal leukoencephalopathy

PML is an opportunistic CNS infection caused by JC virus (JCV). It carries a 20–25% mortality rate. Risk is increased if there has been prior immunosuppression use (not including immunomodulation with IFN-β or glatiramer), with longer duration of natalizumab treatment (especially >2 years), with higher JCV antibody index values and JCV seropositivity (which reflects prior exposure to JCV and is present in ~50% of the population).

Anti-JCV antibody assays are taken prior to therapy to assess PML risk. A negative result is associated with a risk of one case of PML per 10 000 patients treated with natalizumab (for at least 18 months). Patients positive for anti-JCV antibody are at increased risk (see risk stratification in Table A.93). Seroconversion from JCV-negative to positive status occurs at a rate of 1–2% per annum, so JCV status must be repeated regularly (current recommendation is every 6 months) throughout treatment to accurately estimate risk.

MRI is performed before treatment and is repeated annually in low-risk patients (JCV negative or treatment duration <2 years) and 6-monthly in higher-risk patients. Patients are screened for symptoms of PML prior to each infusion. Symptoms of PML include subacute onset of behavioural change or neuropsychiatric symptoms, aphasia, hemiparesis, hemianopia, and seizures.

If PML is suspected, treatment is withheld, and MRI brain plus gadolinium and CSF examination for JCV are performed. If PML is confirmed, plasma exchange is instituted immediately (to remove active drug as soon as possible). Early recognition, early termination of natalizumab, and younger patients, with less co-morbidities are probably associated with better outcomes. On rapid removal of natalizumab, ~90% of patients will develop immune reconstitution inflammatory syndrome (IRIS) of varying severity requiring an extended course of corticosteroids. This usually occurs within days–weeks of PLEX and most will recover from this, or have started to recover by 6 months.

Pharmacokinetics and interactions

Pharmacokinetics

Natalizumab rapidly distributes within the intravascular volume, and steady-state concentrations are reached at 36 weeks. Clearance is unaffected by age, gender, or renal or hepatic function; however, antibodies against natalizumab can increase clearance 3-fold. Natalizumab has a half-life of 16 days. Treatment effects persist for up to 12 weeks.

Interactions None

Table A.93 PML risk stratification for anti-JCV antibody-positive patients (as of 2016)

Natalizumab exposure	Without prior immunosuppression	With prior immunosuppression
0–2 years	<1/1000	1 per 1000
2–4 years	3 per 1000 (1 in 333)	12 per 1000 (1 in 83)
4–6 years	6 per 1000 (1 in 167)	13 per 1000 (1 in 77)

Source data from ℞ www.tysabri.com.

References

Miller DH, Khan OA, Sheremata WA, *et al*.; International Natalizumab Multiple Sclerosis Trial Group. A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2003;**348**(1):15–23.

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Nimodipine

Nimodipine is an orally administered calcium channel blocker that has an increased selectivity for cerebral arterioles. It is the only agent licensed to prevent cerebral vasospasm following aneurysmal subarachnoid haemorrhage (SAH). Nimodipine was first marketed in the UK in the late 1980s.

Uses

Licensed uses

In the UK/USA

- SAH: nimodipine is licensed for the prevention and treatment of ischaemic neurological deficits following aneurysmal SAH in individuals aged 18 years and older.

Off-licence uses

- Reversible cerebral vasoconstriction syndrome (RCVS).

Presentation

- *Trade names*: Nimotop® and Nymalize®. Generics are not available.
- *Formulations*: nimodipine is available as a solution for infusion and a tablet. Tablet: 30mg. Solution for infusion: 50mL vial at 0.02%.

Mechanism of action

Nimodipine is a dihydropyridine L-type calcium channel receptor antagonist. In contrast to other calcium channel blockers, nimodipine has a higher affinity for the cerebral circulation. It acts to enhance cerebral perfusion, particularly in poorly perfused areas, and hence reduces the ischaemic effects arising secondary to vasospasm in SAH.

Toxicity and side effects

- *Common—cardiovascular*: hypotension and variation in heart rate. *Dermatological*: rash and sweating. *Gastrointestinal*: nausea. *Neurological*: headache. *Ophthalmological*: visual disturbance.

Contraindications

- *Absolute*: hypersensitivity to nimodipine or its excipients and within 1 month of MI or an episode of unstable angina. Acute porphyria.
- *Relative*: traumatic SAH (there is no evidence of benefit in this subgroup). In hepatic cirrhosis, the elimination may be reduced; hence the BP needs to be carefully monitored, and the dose reduced, if necessary. No dose adjustment is required in renal impairment, but renal function should be monitored if using an infusion.

Uses in special populations

- *Elderly*: no dose adjustment is routinely required, but an age-related decline in hepatic and renal function, co-prescription of interacting medications, and an increased risk of hypotensive side effects means nimodipine should be used with caution in this group.
- *Pregnancy*: teratogenic effects have been noted in animal studies. Only use if the benefits outweigh the risks.
- *Lactation*: nimodipine is present in mammalian milk and hence should be avoided in nursing mothers.

Efficacy

The British aneurysm nimodipine trial investigated the use of nimodipine (60mg every 4h for 21 days) in patients with a confirmed diagnosis of SAH. The incidence of infarction was 22% vs 33% with placebo, a statistically significant RRR of 33% (95% CI 13–50%). Those treated with nimodipine also had significantly improved neurological outcomes. The findings in this study were reinforced in a meta-analysis that assessed the safety and efficacy of prophylactic nimodipine in patients with SAH; the meta-analysis demonstrated a 48% reduction in cerebral infarcts and a 38% reduction in the onset of delayed neurological deficits. Nimodipine is also used in RCVS, although formal trials in this disorder are not available.

Dosing and monitoring

Dosing

For use in SAH, nimodipine should be started within 96h of SAH at a dose of 60mg every 4h and continued for 21 days.

Monitoring BP and heart rate should be monitored initially, particularly in patients with hepatic impairment.

Pharmacokinetics and interactions

Pharmacokinetics

Bioavailability is 13%, due to extensive first-pass metabolism. T_{max} is ~30–60min. Co-ingestion of food reduces bioavailability and T_{max}. Over 95% of nimodipine is bound to plasma proteins. It is extensively hepatically metabolized, predominantly by the CYP3A4 isoenzyme, to inactive or weakly active metabolites. The plasma half-life is 1.7h. 50% of metabolites are excreted in urine and 30% in faeces.

Interactions See Table A.94.

Table A.94 Interactions of nimodipine

Medications which alter nimodipine plasma levels	Pharmacodynamic interactions
Levels decreased: rifampicin **Levels increased:** cimetidine and grapefruit juice	**With hypotensive agents, e.g. ACE inhibitors:** enhanced hypotensive effect

References

Liu G, Luo J, Zhang L, *et al*. Meta-analysis of the safety and efficacy of prophylactic use of nimodipine in patients with an aneurysmal subarachnoid haemorrhage. *CNS Neurol Disord Drug Targets* 2011;**10**(7):834–44.

Pickard J, Murray G, Illingworth M. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. *BMJ* 1989;**298**(6674):636–42.

Paroxetine

Paroxetine was first marketed in the UK in 1990. Evidence for its use in sleep disorders is solely derived from case study evidence and clinical experience. These studies have suggested differing effects on various sleep disorders, i.e. frequently cited as worsening features of RBD, while improving the symptoms of insomnia and night terrors. It is far more commonly used for psychiatric indications. It benefits from od dosing and an absence of the sedative side effects seen with benzodiazepines; however, it is associated with risks of psychiatric adverse events, including suicidality and a withdrawal syndrome if treatment is ceased abruptly.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- Paroxetine is licensed for a wide range of psychiatric disorders, including depression and anxiety. There is no licensed neurological use.

Off-licence uses

- Insomnia and non-REM parasomnias, e.g. night terrors, sleep walking.

Presentation

- *Trade names*: Brisdelle®, Paxil®, Paxil CR®, Pexeva®, and Seroxat®. Generics are available.
- *Formulations*: paroxetine is available as a capsule, an extended-release tablet, an oral suspension, and a standard tablet. Capsule: 7.5mg. Extended-release tablet: 12.5mg, 25mg, and 37.5mg. Oral suspension: 150mL vial (10mg/5mL). Standard tablet: 10mg, 20mg, and 30mg.

Mechanism of action

Paroxetine is a strong and selective inhibitor of serotonin uptake. The mechanism behind its effects on sleep disorders is not understood. SSRIs as a group can manipulate sleep architecture—they inhibit REM sleep and may result in sleep fragmentation. Sleep disorders are commonly associated with anxiety and depression; potentially, part of its mechanism may be through improvement in these underlying disorders. However, in case reports where paroxetine has been effective at treating night terrors—clinical impact is often after the first dose, rather than weeks to months later, as seen with depression.

Toxicity and side effects

- *Common—dermatological*: sweating. *Gastrointestinal*: anorexia, changes in bowel habit and weight, dry mouth, nausea, and vomiting. *Genitourinary*: sexual dysfunction. *Metabolic*: increased cholesterol and hyponatraemia. *Neurological*: dizziness, headache, impaired concentration, insomnia, and tremor. *Ophthalmological*: blurred vision. *Psychiatric*: abnormal dreams, agitation, fatigue, and SSRI discontinuation syndrome (>30% of patients if treatment is stopped abruptly).

- *Serious—dermatological*: angio-oedema, Stevens–Johnson syndrome, and toxic epidermal necrolysis have been reported. *Gastrointestinal*: hepatitis associated with liver failure has been reported. *Neurological*: serotonin syndrome is very rare. *Ophthalmological*: acute glaucoma has been reported. *Psychiatric*: mania and suicidality have been reported.

Contraindications

- *Absolute*: hypersensitivity to the active drug or its excipients, patients in the manic phase of bipolar affective disorder and with concomitant use of linezolid (only to be continued in exceptional circumstances, with adequate monitoring for serotonin syndrome) and MAOIs (do not start an SSRI until 2 weeks after MAOI cessation).
- *Relative*: cardiac disease, diabetes mellitus, epilepsy (can lower seizure threshold), history of angle-closure glaucoma, bleeding disorders, and mania. In patients with severe hepatic or renal impairment, use reduced doses.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function, and may benefit from lower dosing regimens. In addition, bleeding and hyponatraemia are commoner side effects in the elderly population.
- *Pregnancy*: human epidemiological studies have suggested an increased risk of cardiac septal defects when paroxetine is used in the first trimester, at a rate of ~2/100 vs ~1/100 in the general population. When used in the third trimester, neonates should be monitored for serotonergic/withdrawal effects, including difficulty sleeping, hypoglycaemia, irritability, respiratory distress, and seizures. The risk of primary pulmonary hypertension in the newborn may also be increased 5-fold to an incidence of 1/200. Treatment should be avoided in pregnancy, where possible.
- *Lactation*: paroxetine is present in very low quantities in breast milk <4ng/mL. No side effects have been observed in infants of nursing mothers taking paroxetine; hence use can be considered.

Efficacy

Evidence for use of paroxetine in non-REM parasomnias is derived primarily from case studies and clinical experience. One case series of six patients published in 1997 demonstrated that, in patients treated with between 20mg and 40mg of paroxetine, half of patients had complete cessation of night terrors; the other three patients had reduction, but not complete cessation, of night terrors.

Dosing and monitoring

Dosing

Trial data suggest initiation should be similar to that used in dosing paroxetine for the management of depression and other psychiatric disorders. Start treatment at 10mg od in the morning, and increase to a maximum of 40mg daily, by 10mg steps.

Routine monitoring

Patients should be monitored for psychiatric adverse events, specifically suicidality, in the first few months of treatment.

Pharmacokinetics and interactions

Pharmacokinetics

Paroxetine undergoes substantial first-pass metabolism. This mechanism is saturable to some extent, giving non-linear kinetics to paroxetine absorption and rendering absolute bioavailability of different formulations difficult to assess. Food co-ingestion in single-dose studies reduced time to peak plasma concentration from 6.4h to 4.9h. Peak plasma concentration was ~30% higher with food. Steady state is reached at ~10 days. More than 90% is protein-bound.

Paroxetine is extensively hepatically metabolized, predominantly into conjugates with glucuronic acid and sulfate. These are pharmacologically inactive. Metabolism is partially undertaken by CYP2D6 which can become saturated and results in non-linear kinetics of paroxetine metabolism. The elimination half-life is ~21h. Two-thirds of the drug is excreted by the kidneys, and the other third in the faeces; only 2% is excreted as the parent compound.

Interactions See Table A.95.

Table A.95 Interactions of paroxetine

Medications which alter paroxetine plasma levels	Medications whose plasma levels are altered by paroxetine	Pharmacodynamic interactions
Levels decreased: CYP2D6 inducers, e.g. rifampicin	**Levels decreased:** endoxifen, an active metabolite of tamoxifen synthesized through CYP2D6 metabolism	**With serotonergic medications, e.g. linezolid, tramadol, etc.:** increased risk of serotonergic syndrome
Levels increased: CYP2D6 inhibitors, e.g. cimetidine	**Levels increased:** drugs metabolized by CYP2D6, e.g. anticoagulants, metoprolol, pimozide, procyclidine, risperidone, and TCAs	**With drugs known to increase bleeding risk, e.g. atypical antipsychotics, NSAIDs, TCAs:** increased risk of bleeding **With MAOIs, including linezolid:** increased risk of hypertensive crisis

References

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Wilson SJ, Nutt DJ, Alford C, *et al*. British Association for psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. *J Psychopharmacol* 2010;**24**(11):1577–600.

Penicillamine

Penicillamine was first marketed in the UK in 1987. It was one of the first drugs to be used in the management of WD and acts as a copper chelator, lowering total body copper content. It is effective in this respect but carries a high rate of side effects, and use by neurologists is complicated by the fact that, in patients presenting with neurological symptoms of WD, penicillamine can paradoxically make these symptoms worse in 5–22% of patients.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- *Inborn errors of metabolism*: penicillamine is licensed for the treatment of WD in individuals of all ages.

Off-licence uses

- None.

Presentation

- *Trade names*: Cuprimine®, Depen®, and Distamine®. Generics are available in the UK.
- *Formulations*: penicillamine is available as a capsule and a tablet. Tablet: 125mg and 250mg. Capsule: 250mg.

Mechanism of action

WD is characterized by the accumulation of copper in the liver, brain, and other tissues. This occurs secondary to the impaired function of ATP7B, an enzyme required to bind copper to caeruloplasmin, allowing the release of copper into the bloodstream. Penicillamine is a copper-chelating agent, which binds copper atoms and is subsequently excreted by the urinary tract, thereby reducing total systemic levels of copper.

Toxicity and side effects

- *Common—gastrointestinal*: anorexia, diarrhoea, nausea, and vomiting. *Immunological*: fever, lymph node enlargement, and rash in 30%.
- *Serious—dermatological*: elastosis perforans, pseudoxanthoma elasticum, urticaria (all rare). *Haematological*: thrombocytopenia is common, and regular monitoring should be undertaken. Agranulocytosis, neutropenia, and aplastic anaemia are rare. *Immunological*: Goodpasture's syndrome, lupus-like reaction, MG, and nephrotic syndrome. *Neurological*: neuropathy is rare (see below), and prophylactic pyridoxine is often co-prescribed for patients with poor dietary intake, as penicillamine increases the requirement for this vitamin. In up to a quarter of cases where penicillamine therapy is initiated, deterioration of the neurological features of WD (rigidity, dystonia, dysarthria, and tremor) can occur over a period of 2 weeks to 12 months (commonly after 6 weeks). This may be due to the mobilization and redistribution of copper from the liver to the brain. *Renal*: proteinuria is common, and

patients should have regular urinalysis. Haematuria is rare, but the drug must be withdrawn immediately if no alternative cause is idenitified.
Respiratory: dyspnoea, pulmonary haemorrhage, and pulmonary fibrosis have been reported.

Contraindications

- *Absolute*: hypersensitivity to penicillamine, previous agranulocytosis, aplastic anaemia, or thrombocytopenia with penicillamine, lupus erythematosus, and moderate or severe renal impairment.
- *Relative*: concomitant use of nephrotoxic drugs and gold treatment. In addition, use with caution if previous adverse reactions to gold.

In patients with mild renal impairment, use with caution, and regularly monitor renal function. No dose adjustment is required in hepatic impairment.

Uses in special populations

- *Elderly*: elderly patients are more likely to have both age-related renal impairment and to experience adverse effects related to penicillamine treatment. Start treatment at 20mg/kg daily in divided doses, and use the smallest possible dose to control symptoms.
- *Pregnancy*: penicillamine has been shown to be teratogenic in rats. There are no human controlled studies. There have been anecdotal reports of human congenital abnormalities, and hence it should be avoided in pregnancy, if possible.
- *Lactation*: it is not known if penicillamine is excreted in breast milk, and the manufacturer advises to avoid use in nursing mothers.

Efficacy

Even though high-quality evidence regarding the efficacy of initial monotherapy in WD is lacking, clinical consensus and small studies suggest that penicillamine is the most effective treatment for patients with hepatic presentation of WD. Evidence suggests that the majority of patients in the preclinical stages of WD or with a neurological presentation show favourable clinical outcomes (remain asymptomatic or improve) when treated with D-penicillamine on a long-term basis; a systematic review showed favourable clinical outcomes in 80.6% of patients with neurological symptoms of WD. However, as mentioned above, a significant proportion of patients (5.3–22%) may show neurological deterioration soon after initiation of therapy with D-penicillamine.

Dosing and monitoring

Dosing

Start treatment at 1500–2000mg daily in divided doses. Drug efficacy is optimized when used in conjunction with a low-copper diet (below 1mg of copper per day). A maximum daily dose of 2000mg should not be continued for >1 year, and once there is a good response, the dose can be reduced to a maintenance dosing of 750–1000mg daily. An overall negative copper balance (taking into account the analysis of 24h urinary copper excretion and dietary copper intake) is considered a good response.

Routine monitoring Routine monitoring (weekly in the first 2 months and monthly thereafter) of the FBC and urinalysis should be undertaken. If the platelet count falls below 120 000/mm^3 or WBCs below 2500/mm^3 or either parameter shows three consecutive falls within the normal reference range, then withdrawal of penicillamine should be considered. The drug can be restarted at a lower dose, once counts return to the normal range.

Pharmacokinetics and interactions

Pharmacokinetics

Bioavailability is 40–70%. T_{max} is 1–3h. Co-ingestion of food reduces bioavailability. It is 80% plasma protein-bound and is eliminated primarily by metabolism to a disulfide form before excretion in the urine. The half-life is 1–3h.

Interactions See Table A.96.

Table A.96 Interactions of penicillamine

Medications which alter penicillamine plasma levels	Medications whose plasma levels are altered by penicillamine	Pharmacodynamic interactions
Levels decreased: oral antacids or iron (administered within 2h) and zinc	**Levels decreased:** digoxin (administered within 2h) and zinc **Levels increased:** levodopa	**With gold or immunosuppressants:** increased risk of blood dyscrasias **With NSAIDs:** increased risk of renal impairmement

References

Chang H, Xu A, Chen Z, *et al*. Long-term effects of combination of D-penicillamine and zinc salts in the treatment of Wilson's disease in children. *Exp Ther Med* 2013;**5**(4):1129–32.

Czlonkowska A, Gajda J, Rodo M. Effects of long-term treatment in Wilson's disease with D-penicillamine and zinc sulphate. *J Neurol* 1996;**243**(3):269–73.

Weiss KH, Thurik F, Gotthardt DN, *et al*. Efficacy and safety of oral chelators in treatment of patients with Wilson disease. *Clin Gastroenterol Hepatol* 2013;**11**(8):1028–35.

Wiggelinkhuizen M, Tilanus ME, Bollen CW, *et al*. Systematic review: clinical efficacy of chelator agents and zinc in the initial treatment of Wilson disease. *Aliment Pharmacol Ther* 2009;**29**(9):947–58.

Perampanel

Perampanel was first marketed for use as an AED in the UK in 2012. It was initially licensed as an adjunct in focal onset epilepsy but has recently also demonstrated efficacy and been licensed for the management of primary generalised tonic-clonic seizures in drug-resistant patients.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- *Epilepsy*: perampanel is licensed as an adjunct for the treatment of focal-onset seizures and as an adjunct for primary generalised tonic-clonic seizures (in the context of idiopathic generalised epilepsy) in individuals aged 12 years and older.

Off-licence uses

- None.

Presentation

- *Trade names*: Fycompa®. Generics are not available.
- *Formulations*: perampanel is available as a film-coated tablet. Tablet: 2mg, 4mg, 6mg, 8mg, 10mg, and 12mg.

Mechanism of action

Perampanel selectively and non-competitively inhibits AMPA receptors. These are ion channels that open in response to glutamate and other mediators of rapid excitatory neurotransmission. *In vitro* and *in vivo* models show that AMPA receptor antagonists have potent antiepileptic activity. At high concentrations, perampanel also weakly inhibits NMDA receptors, which may also contribute to seizure suppression.

Toxicity and side effects

- *Common—gastrointestinal*: changes in appetite and nausea are common. Weight may increase. *Musculoskeletal*: back pain. *Neurological*: dizziness and fatigue are the commonest side effects requiring discontinuation. Ataxia, confusion, dysarthria, and falls can also occur. *Ophthalmological*: blurred and double vision. *Psychiatric*: aggression and anxiety.
- *Serious*: *Dermatological*: Drug related eosinophilia and systemic side effects. *Psychiatric*: Homicidal and suicidal thoughts (tend to be dose-related and usually occur in first 6 weeks—can be exacerbated by alcohol.)

Contraindications

- *Absolute*: hypersensitivity to perampanel or any of its excipients.
- *Relative*: perampanel is associated with hostility and suicidality it should be used with caution in patients with significant psychiatric disturbance. It is not recommended in moderate to severe renal impairment. No dose adjustment is currently recommended for mild renal impairment. Use in severe hepatic dysfunction is not recommended. In mild to moderate hepatic dysfunction, doses should be uptitrated no faster than fortnightly, and the maximum recommended dose is 8mg/day.

Uses in special populations

- *Elderly*: the elderly appear to be particularly at risk of falls as a side effect, and hence this should be monitored for. Caution should be used in the context of polypharmacy to ensure potential drug interactions are avoided.
- *Pregnancy*: limited data are available. Perampanel is not recommended in pregnant women. There have been no documented impairments to fertility in animal studies. There are no data about drug pharmacokinetics in pregnancy.
- *Lactation*: perampanel is excreted into mammalian milk. Its presence in human milk has not yet been evaluated. Risks to the infant are unknown. Breastfeeding can continue if benefits outweigh risks.

Efficacy

Results of a phase 3 clinical trial (a multicentre, double-blind, placebo-controlled trial in patients >12 years old) suggest that, as an adjunct in focal-onset epilepsy, 8mg o f perampanel resulted in a >50% reduction in seizure frequency in one-third of patients vs 15% with placebo. A double-blind placebo controlled study investigating the use of perampanel in the treatment of refractory primary generalized tonic-clonic seizures demonstrated a 50% responder rate of 58% vs 35.8% in the placebo group ($p = 0.0059$). The dose trialled was 8mg or highest tolerated.

Dosing and monitoring

Dosing

Start treatment at 2mg/day in an once-daily dose prior to bedtime. This can be increased by increments of 2mg/day fortnightly, unless perampanel is to be co-administered with medications which act to shorten its half-life (see Table A.95). If this is the case, then titration intervals of 1 week should be used. The normal maintenance dose is 4–8mg/day, although a maximum of 12mg/day can be used.

Routine monitoring Renal and hepatic function should be assessed prior to starting treatment, particularly in the elderly.

Therapeutic drug monitoring There are no data as yet relating plasma perampanel levels with that of seizure suppression or adverse effects.

Pharmacokinetics and interactions

Pharmacokinetics

Perampanel has an oral bioavailability of ~100%. The rate of absorption, but not the extent of absorption, is affected by co-ingested food. T_{max} is between 15min and 2h, depending on whether food is co-ingested. Over 95% of perampanel is bound to plasma proteins. Steady state is reached in 2 weeks. Less than 2% of the medication is excreted unchanged in the urine. The rest is extensively hepatically metabolized by sequential oxidation, primarily via CYP3A4, then by glucuronidation. 70% of the metabolized product is excreted in the faeces, the rest via the renal system. The half-life is ~105h. This is shortened to ~25h by carbamazepine, and the clearance of perampanel is doubled by phenytoin and oxcarbazepine, and, to a lesser extent, by topiramate. Mild to moderate hepatic dysfunction lengthens the half-life to ~300h.

Interactions See Table A.97.

Table A.97 Interactions of perampanel

Medications which alter perampanel plasma levels	Medications whose plasma levels are altered by perampanel	Pharmacodynamic interactions
Levels decreased: carbamazepine, oxcarbazepine, phenytoin, and topiramate **Levels increased:** ketoconazole	**Levels decreased:** carbamazepine, clobazam, lamotrigine, oxcarbazepine (metabolite not measured), and valproate	**With alcohol:** can lead to aggression, confusion, and low mood

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Phenobarbital

Phenobarbital was first marketed in the UK as an AED in 1912. It is one of the oldest antiepileptic medications still in widespread use. In developing countries, the WHO have recommended its use first-line in most seizure types. In developed countries, it has been largely relegated to third-line behind benzodiazepines and phenytoin in the treatment of status epilepticus. It is a very effective broad-spectrum AED. Its main advantage is its swift onset of action when given IV or IM. It also has a long half-life, allowing for once-daily dosing. Tolerance does not occur. Its disadvantages are its marked sedative and behavioural side effects, the need for frequent blood monitoring, and its significant pharmacokinetic interaction profile.

Uses

Licensed uses

In the UK/USA

- *Epilepsy*: phenobarbital is licensed for the treatment of all forms of epilepsy (UK: except absence seizures) in individuals of all ages.

Off-licence uses

- None.

Presentation

- *Trade names*: Luminal®. Generics are available.
- *Formulations*: phenobarbital is available as an elixir, an oral solution, a solution for IV injection, and a tablet. Elixir: 15mg/5mL. Oral solution: 20mg/5mL. Solution for IM or IV injection: 15mg/mL, 30mg/mL, 60mg/mL, and 200mg/mL in 1mL ampoules.

Mechanism of action

The primary mechanism of action of phenobarbital is probably through prolongation of the opening times of chloride ion channels in post-synaptic neuronal membranes. This acts to enhance GABA-mediated inhibition throughout the cerebrum. Some of its actions may also be mediated by decreasing intraneuronal sodium concentrations, inhibiting calcium influx following neuronal depolarization, raising serotonin levels, and inhibiting NA uptake.

Toxicity and side effects

- *Common—dermatological*: maculopapular rashes in 1–3%. *Endocrine*: osteopenia with long-term use. *Gastrointestinal*: cholestasis. *Genitourinary*: loss of libido and erectile dysfunction. *Neurological*: patients commonly experience a dose-dependent ataxia, cognitive impairment, drowsiness, dysarthria, lack of coordination, and nystagmus. This is reversible on withdrawal of the drug. The most frequent side effect in adults is sedation. The elderly are prone to hyperactivity and irritability. *Psychiatric*: depression.
- *Serious—dermatological*: rarely, hypersensitivity reactions, such as Stevens–Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme, can occur. *Gastrointestinal*: hepatitis can

occur. *Haematological*: attacks of acute intermittent porphyria and agranulocytosis. *Immunological*: widespread multisystem hypersensitivity reactions can occur. *Psychiatric*: suicidal ideation has been reported. *Respiratory*: respiratory depression can occur.

Of note, uncommonly, anaemia and thrombocytopenia can occur, often related to folate deficiency, can result. In addition, long-term use can result in diffuse musculoskeletal pain, Dupuytren's contracture, frozen shoulder, plantar fibromatosis, heel and knuckle pads, and Peyronie's syndrome.

Contraindications

- *Absolute*: acute intermittent porphyria, known hypersensitivity to barbiturates or its excipients, severe hepatic impairment, severe renal impairment, and severe respiratory depression.
- *Relative*: it is ineffective in the management of absence seizures. Caution in individuals at risk of osteopenia (they may benefit from prophylactic calcium and vitamin D supplements) and individuals with a mild to moderate degree of respiratory depression, and when treating children or the elderly. Lower doses of phenobarbital should be used in mild to moderate hepatic and renal impairment.

Uses in special populations

- *Elderly*: the elderly are more susceptible to the sedative action of phenobarbital. In addition, they have an age-related deterioration in their renal and hepatic function, and hence benefit from lower dosing regimens.
- *Pregnancy*: there is clear evidence of risk to the fetus. Vitamin K-deficient haemorrhagic disease of the newborn can be prevented by prophylactic treatment with vitamin K. Use in pregnancy involves weighing up potential benefits and side effects (see Antiepileptic drugs in young women, pp. 37–9).
- *Lactation*: phenobarbital is present in breast milk. Infant plasma levels can be 50–100% of the mother's. If used, infants should be monitored for potential side effects such as sedation, vomiting, not reaching milestones, and weight gain. Infant plasma levels can be assessed, and the infant switched to an alternative feeding regimen if side effects are identified.

Efficacy

There are very limited research data about the efficacy of phenobarbital in developed countries. In developing countries, the effectiveness of phenobarbital as a monotherapy in the treatment of multiple seizure types has been repeatedly demonstrated. Its advantage in these settings is its low cost. A recent study from an epilepsy clinic in north India showed that a year's treatment amounted to 11 American dollars, a quarter of the price of valproate and dramatically cheaper than the newer AEDs.

Dosing and monitoring

Dosing

The long half-life and slow accumulation of phenobarbital means that maintenance doses can be given on the first day.

- *For the treatment of all forms of epilepsy, except typical absence seizures*, age >18 years: start treatment at 1.5–4mg/kg/day in once-daily doses at night. Maintenance dose is usually between 60 and 180mg/day.
- *For the treatment of status epilepticus*: the loading dose should be 10mg/kg at a maximum rate of 10mg/min. The solution for IV injection needs to be first diluted by 1 in 10 with water for injections.

Routine monitoring FBC and LFTs can be considered prior to starting phenobarbital, but regular monitoring is usually not necessary. Vitamin D level, with dual-energy X-ray absorptiometry (DEXA) scans, is indicated for individuals at risk of osteoporosis.

Therapeutic drug monitoring Optimum seizure control, when used in monotherapy, occurs at plasma concentrations of 10–40mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

Bioavailability is >90% via both PO and IM routes. Food co-ingestion can delay absorption but does not impact on bioavailability. T_{max} occurs in <4h for both PO and IM injections. Fifty-five per cent is protein-bound within the plasma. Up to 80% of phenobarbital is metabolized by the cytochrome P450 system. There is a degree of autoinduction (CYP1A2, CYP2C9, CYP2C19, and CYP3A4); hence, if phenobarbital is used as monotherapy, the dose may need to be increased when steady state is reached at 2–3 weeks. The half-life is 70–140h in adults. The two main metabolites are *p*-hydroxyphenobarbital and 9-*D*-glucopyranosylphenobarbital. These are both inactive and, following further metabolism, are renally excreted. ~25% of phenobarbital is eliminated unchanged in the urine.

Interactions See Table A.98.

Table A.98 Interactions of phenobarbital

Medications which alter phenobarbital plasma levels	Medications whose plasma levels are altered by phenobarbital	Pharmacodynamic interactions
Levels decreased: antacids **Levels increased:** chloramphenicol, dicoumarol, and propoxyphene	**Levels decreased:** substrates of CYP1A2, CYP2C9, CYP2C19, and CYP3A4 enzymes, including albendazole, indinavir, ketoconazole, lamotrigine, and warfarin **Levels increased:** retigabine	**With alcohol:** can lead to aggression, confusion, and low mood

References

Krishnan A, Sahariah SU, Kapoor SK. Cost of epilepsy in patients attending a secondary-level hospital in India. *Epilepsia* 2004;**45**(3):289–91.

Meierkord H, Boon P, Engelsen B, *et al*.; European Federation of Neurological Societies. EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol* 2010;**17**(3):348–55.

Tudur Smith C, Marson AG, Williamson PR. Carbamazepine versus phenobarbitone monotherapy for epilepsy. *Cochrane Database Syst Rev* 2003;**1**:CD001904.

Piracetam

Piracetam has been available in the UK since the 1970s. It is particularly useful in the treatment of myoclonic seizures and may be the only effective medication in some patients with progressive myoclonic epilepsy syndromes. It has a good adverse effect and pharmacokinetic profile but is a narrow-spectrum agent, with only limited efficacy in myoclonic syndromes.

Uses

Licensed uses

In the UK

- *Epilepsy*: piracetam is licensed for the treatment of myoclonus of cortical origin, regardless of the aetiology, in individuals aged 16 years and older.

Piracetam is not licensed for use in the USA.

Off-licence uses

- None.

Presentation

- *Trade names*: Myocalm® and Nootropil®. Generics are available.
- *Formulations*: piracetam is available as a film-coated tablet and an oral solution. Film-coated tablet: 800mg and 1.2g. Oral solution: 333.3mg/mL.

Mechanism of action

The mechanism of the anti-myoclonus activity of piracetam is unclear. *In vitro* and *in vivo* studies have demonstrated improved cerebral blood flow and metabolism, anticholinergic effects, reduced platelet aggregation, and enhanced erythrocyte function.

Toxicity and side effects

- *Common—gastrointestinal*: abdominal discomfort, nausea, and weight gain. *Neurological*: hyperkinesia. *Psychiatric*: nervousness.
- *Serious—haematological*: haemorrhagic disorders have rarely been reported. *Psychiatric*: depression and hallucinations.

Contraindications

- *Absolute*: hypersensitivity to piracetam, other pyrrolidone derivatives, or its excipients. Due to its effects on coagulation and platelet action, avoid in cerebral haemorrhage. In addition, avoid in Huntington's chorea. Avoid if eGFR is <20mL/min/1.73m^2.
- *Relative*: caution in individuals at increased risk of bleeding, e.g. major surgery, etc. At eGFR 50–80mL/min/1.73m^2, two-thirds of the normal dose should be used. At eGFR 30–50mL/min/1.73m^2, one-third of the normal dose in two divided doses should be used. At eGFR 20–30mL/min/1.73m^2, one-sixth of the normal dose as a single dose should be used. No dose adjustment is required in hepatic impairment.

Uses in special populations

- *Elderly*: age-related deterioration in renal function means that dosing should be adjusted in line with eGFR values.
- *Pregnancy*: some animal studies have demonstrated teratogenic effects; however, there are no controlled studies in humans. It is not known if piracetam pharmacokinetics change during pregnancy. The manufacturer advises avoidance in pregnancy.
- *Lactation*: the manufacturer advises avoidance in breastfeeding. If used, infants should be monitored for potential side effects such as fatigue and irritability. The infant should be switched to an alternative feeding regimen if these are identified.

Efficacy

There are limited clinical data on the efficacy of piracetam in the treatment of myoclonus. One multicentre, double-blind, cross-over trial showed marked improvement in patients suffering from progressive myoclonic epilepsy syndromes. The effects of piracetam were reported as rapid and long-lasting.

Dosing and monitoring

Dosing

Start treatment at 7.2g daily in 2–3 divided doses. This can be increased by 4.8g every 2–3 days up to a recommended maximum of 24g daily. The normal maintenance dose is <20g/day.

Routine monitoring Coagulation, and renal and hepatic function should be assessed at baseline and repeated every 6–12 months.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is ~100% and is not affected by food co-ingestion. T_{max} occurs at 0.5–1.5h post-dose. Steady state is reached in 1–2 days. There is no protein binding. ~100% of piracetam is excreted unchanged by the renal system. The half-life is ~5h.

Interactions See Table A.99.

Table A.99 Interactions of piracetam

Pharmacodynamic interactions
With thyroxine: may result in confusion
With anticoagulants and antiplatelets: increased risk of bleeding

References

Brown P, Steiger MJ, Thompson PD, *et al*. Effectiveness of piracetam in cortical myoclonus. *Mov Disord* 1993;**8**(1):63–8.

Koshkiniemi M, Van Vleyman B, Hakamies L, *et al*. Piracetam relieves symptoms in progressive myoclonus epilepsy: a multicentre, randomised, double-blind, crossover study comparing the efficacy and safety of three dosages of oral piracetam with placebo. *J Neurol Neurosurg Psychiatry* 1998;**64**(3):344–8.

Pizotifen

Pizotifen is an antihistamine that has both serotonin antagonist and antimuscarinic effects. It was developed in the late 1960s as a prophylactic agent in migraine and cluster headache. It can take several weeks before an effect is seen, and use is limited by adverse effects, specifically anticholinergic effects, sedation, and weight gain.

Uses

Licensed uses

In the UK

- *Vascular headache*: pizotifen is licensed for use in the prevention of vascular headache, which includes migraine and cluster headache, in individuals aged 2 years and older.

Pizotifen is not licensed for use in the USA.

Off-licence uses

- None.

Presentation

- *Trade names*: Pizotyline®, Sanomigran®. Generics are available.
- *Formulations*: it is available as a tablet and an elixir. Tablets: 0.5mg and 1.5mg. Elixir: 0.25mg/5mL.

Mechanism of action

The mechanism of action of pizotifen is unclear. It has antagonistic activity at the $5HT_2$ receptor, but this is unlikely to underlie its antimigraine effect, as other drugs with a similar action have no effect on migraine. It also has antihistaminergic (H1), antimuscarinic, anti-adrenergic effects ($\alpha 1$ and $\alpha 2$), and antidopaminergic effects, but specific antagonists at these receptors have also failed to show benefit in migraine.

Toxicity and side effects

- *Common—endocrine*: increased appetite, weight gain. *Gastrointestinal*: dry mouth and nausea. *Neurological*: sedation.
- *Serious—cardiac*: fluid retention. *Neurological*: seizures.

Contraindications

- *Absolute*: hypersensitivity to pizotifen.
- *Relative*: it should be used with caution in porphyria, and history of acute angle-closure glaucoma, epilepsy, and urinary retention. It can be used in hepatic and renal impairment, but patients should be monitored closely. Slower dose uptitration may be needed.

Uses in special populations

- *Elderly*: elderly patients can receive the same dose as younger patients but may require closer monitoring, due to greater susceptibility to the antimuscarinic effects of pizotifen.

- *Pregnancy*: animal studies have not shown harmful effects from pizotifen, but data on its effects in human pregnancy are limited, and so pizotifen should only be used if the potential benefit outweighs the risk of harm.
- *Lactation*: pizotifen is found in breast milk and should be avoided.

Efficacy

Pizotifen has been shown to be superior to placebo in migraine prophylaxis in several randomized-controlled, double-blind studies. It reduces the frequency of migraine and the amount of antimigraine treatment needed in the acute attack. In one randomized study, 70% of the patients in the pizotifen arm found a very good or good effect from using pizotifen, compared with only 11% in the placebo arm.

Dosing and monitoring

Dosing

Start treatment at 0.5mg. This can be increased at 2- to 3-weekly intervals to a maximum daily dose of 4.5mg which should be given in divided doses. No single dose should exceed 3mg. The usual dose is 1.5mg daily, taken as a single dose at night or in three divided doses.

Routine monitoring Monitor weight, and regularly review for sedative side effects.

Pharmacokinetics and interactions

Pharmacokinetics

Pizotifen has an oral bioavailability of 80%. Peak serum concentration is reached ~5h after ingestion. More than 90% of the drug is protein-bound. Pizotifen undergoes extensive hepatic metabolism, mainly glucuronidaton, and its main metabolite is *N*-glucuronide conjugate. It does not induce or inhibit the cytochrome P450 system. Co-ingestion of food does not affect bioavailability. 18% of the parent drug is excreted unchanged in the faeces; <1% of the drug is excreted unchanged renally. The remainder is excreted as metabolites, 62% in the urine and 24% in the faeces. The half-life is 26h.

Interactions See Table A.100.

Table A.100 Interactions of pizotifen

Pharmacodynamic interactions
With anticholinergics: enhanced cholinergic effect
With sedatives (alcohol, antipsychotics): increased sedation

References

Osterman P. A comparison between placebo, pizotifen and divascan in migraine prophylaxis. *Acta Neurol Scand* 1977;**56**(1):17–28.

Symon DN, Russell G. Double blind placebo controlled trial of pizotifen syrup in the treatment of abdominal migraine. *Arch Dis Child* 1995;**72**(1):48–50.

Pregabalin

Pregabalin was first marketed in the UK in 2004. It is a GABA analogue, designed to be more effective than gabapentin. It is licensed for use in epilepsy and neuropathic pain. It is well tolerated, has few pharmacokinetic interactions, and may be more effective than gabapentin for both indications.

Uses

Licensed uses

In the UK/USA

- *Epilepsy*: pregabalin is licensed for treatment as an adjunct of focal-onset seizures in individuals aged 18 years and older.
- *Neuropathic pain*: pregabalin is licensed for peripheral and central neuropathic pain in individuals aged 18 years and older (in the USA, licensing specifies use for post-herpetic neuralgia, painful diabetic peripheral neuropathy, fibromyalgia, and neuropathic pain associated with spinal cord injury).

Off-licence uses

- Insomnia and PLMS.

Presentation

- *Trade names*: Lyrica®. Generics are not available.
- *Formulations*: pregabalin is available as a capsule and an oral solution. Capsule: 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, and 300mg. Oral solution: 20mg/mL.

Mechanism of action

Pregabalin is a GABA analogue which does not act directly on GABA receptors. Its main action is thought to be via binding to, and closing, voltage-gated N and P/Q presynaptic calcium channels, thereby reducing epileptiform activity and synaptic transmission along nociceptive pathways.

Toxicity and side effects

- *Common—endocrine*: sexual dysfunction is common. *Gastrointestinal*: common side effects include appetite changes, dry mouth, constipation, flatulence, nausea, and weight gain. Less commonly, abdominal bloating, hypersalivation, reflux, and taste disturbance can occur. *Neurological*: dizziness and fatigue are the commonest neurological side effects. Less commonly, confusion, dysarthria, insomnia, memory impairment, paraesthesiae, and poor attention can occur. *Ophthalmological*: blurred and double vision. *Psychiatric*: euphoria and irritability.
- *Serious—cardiovascular*: arrhythmias, heart block, heart failure, and QT interval prolongation can rarely occur. *Dermatological*: there are reports of angio-oedema and Stevens–Johnson syndrome. *Gastrointestinal*: rarely, pancreatitis has been reported. *Musculoskeletal*: rarely, rhabdomyolysis has been reported. *Ophthalmological*: reduced visual acuity and visual field defects. *Psychiatric*: suicidal ideation has been reported. *Renal*: renal failure has been reported.

Contraindications

- *Absolute*: hypersensitivity to gabapentin, pregabalin, or any of its excipients.
- *Relative*: pregabalin may exacerbate myoclonus; hence it should be avoided in this context. Emergent myoclonic jerks in the treatment of focal seizures are a sign to stop treatment. Caution in individuals suffering from severe heart failure and in those with conditions where encephalopathy may be precipitated. Pregabalin is predominantly eliminated by the renal system. If eGFR is 30–60mL/min/1.73m^2, the maximum recommended dose is 300mg daily. If eGFR is 15–30mL/min/1.73m^2, start treatment at 25mg od, and increase to a maximum of 150mg daily in 1–2 divided doses. If eGFR is <15mL/min/1.73m^2, start at 25mg od up to a maximum of 75mg od. Dosage adjustment is not necessary in hepatic dysfunction.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal function and may benefit from lower dosing regimens. The elderly are also more at risk of side effects, including confusion, cognitive impairment, falls, and heart block/failure.
- *Pregnancy*: some animal studies have demonstrated teratogenic effects; however, there are no studies in humans. There are currently no data looking at whether the pharmacokinetics of pregabalin change during pregnancy. Use in pregnancy should be avoided where possible.
- *Lactation*: it is not known if pregabalin is present in breast milk. If used, infants should be monitored for potential side effects and switched to an alternative feeding regimen if these are identified.

Efficacy

- *Epilepsy*: a Cochrane review, conducted in 2008, of four trials investigating pregabalin use as an adjunct in refractory focal-onset epilepsy concluded that pregabalin was significantly more effective than placebo. A further Cochrane review in 2012 investigating the use of pregabalin as monotherapy in the treatment of focal-onset epilepsy concluded that pregabalin was inferior, in terms of efficacy, to lamotrigine, although similar with regards tolerability.
- *Neuropathic pain*: a systematic review encompassing 19 studies with 7003 participants found pregabalin effective at doses of 300–600mg in achieving at least 50% pain relief in patients with post-herpetic neuralgia (NNT 3.9, 95% CI 3.1–5.1), painful diabetic neuropathy (NNT 5.0, 95% CI 4.0–6.6), central neuropathic pain (NNT 5.6, 95% CI 3.5–14), and fibromyalgia (NNT 11, 95% CI 7.1–21). Two further systematic reviews have demonstrated that pregabalin was effective in providing pain relief post-spinal cord injury and with phantom limb pain.

Dosing and monitoring

Dosing

- *For all indications*: start treatment at 25mg bd. Then increase at 1-week intervals by 50mg in divided doses to a maintenance dose of 300mg in 2–3 divided doses. It can be increased to a maximum of 600mg in divided doses.

Routine monitoring Hepatic and renal function testing should be monitored at baseline and yearly thereafter. Monitor the weight and BMI; consider assessing fasting cholesterol and glucose at baseline.

Therapeutic drug monitoring Optimum seizure control, when used in monotherapy, occurs at plasma concentrations of 2–8mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

The oral bioavailability is >90%. This is not dependent on the dose or food co-ingestion. T_{max} is faster, ~1h in the fasted state, compared to with food co-ingestion when it is 2.5–3h. Steady-state plasma levels are reached in 1–2 days. Pregabalin is not bound to plasma proteins and is not metabolized by the liver. More than 98% is eliminated unchanged by the renal system. Renal clearance is directly proportional to the eGFR. The half-life is ~6h.

Interactions Table A.101.

Table A.101 Interactions of pregabalin

Medications which alter pregabalin plasma levels	Medications whose plasma levels are altered by pregabalin	Pharmacodynamic interactions
Levels decreased: gabapentin and phenytoin	**Levels decreased:** tiagabine	**With CNS depressants, e.g. alcohol and MAOIs:** can increase sedative side effects

References

Guy S, Mehta S, Leff L, *et al*. Anticonvulsant medication use for the management of pain following spinal cord injury: systematic review and effectiveness analysis. *Spinal Cord* 2014;**52**(2):89–96.

Lozasdi D, Hemming K, Marson AG. Pregabalin add-on for drug-resistant partial epilepsy. *Cochrane Database Syst Rev* 2008;**1**:CD005612.

McCormick Z, Chang-Chien G, Marshall B, *et al*. Phantom limb pain: a systematic neuroanatomical-based review of pharmacological treatment. *Pain Med* 2014;**15**(2):292–305.

Wiffen PJ, Derry S, Moore RA, *et al*. Antiepileptic drugs for neuropathic pain and fibromyalgia – an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2013;**11**:CD010567.

Zhou Q, Zheng J, Yu L, *et al*. Pregabalin monotherapy for epilepsy. *Cochrane Database Syst Rev* 2012;**10**:CD009429.

Primidone

Primidone was first marketed in the UK as an AED in 1952. It is rapidly broken down into its active metabolites: phenobarbital which accounts for the majority of its antiepileptic action, and phenyl-ethyl malonamide (PEMA). Principal disadvantages are sedative and behavioural side effects and its extensive pharmacokinetic interactions. It is occasionally useful when other drugs have failed in the treatment of focal-onset or generalized seizures.

Uses

Licensed uses

In the UK

- *Epilepsy/myoclonus*: primidone is licensed for use as an adjunct or monotherapy in the treatment of akinetic attacks, focal-onset seizures, grand mal epilepsy, Jacksonian seizures, myoclonic jerks, and temporal lobe epilepsy in individuals of all ages.
- *ET*: primidone is licensed for the management of ET in individuals of all ages.

In the USA

- *Epilepsy*: primidone is licensed for use as an adjunct or monotherapy in the treatment of focal-onset, grand mal, and psychomotor seizures in individuals of all ages.

Off-licence uses

- Holmes' tremor.

Presentation

- *Trade names*: Mysoline®. Generics are available.
- *Formulations*: primidone is available as a scored tablet in 50mg and 250mg doses.

Mechanism of action

Primidone is rapidly converted to phenobarbital which accounts for the majority of its antiepileptic action (see Phenobarbital, pp. 555–8). Primidone has also been demonstrated to exert additional seizure protection, independent of phenobarbital. The mechanism for this additional ability and for the effect of primidone in ET has not yet been established.

Toxicity and side effects

In addition to the side effects associated with phenobarbital (see Phenobarbital, pp. 555–8), there is often an initial toxic reaction which arises before phenobarbital or PEMA are detectable in the blood. This comprises ataxia, dizziness, drowsiness, nausea, and vomiting that may be initially debilitating, but a tolerance soon develops.

In addition to phenobarbital-related side effects, the following may occur.

- *Common—gastrointestinal*: nausea and vomiting. *Neurological*: dizziness and headache. *Ophthalmological*: visual disturbances.
- *Serious—immunological*: SLE. *Psychiatric*: psychosis has been reported.

Contraindications

See Phenobarbital, pp. 555–8.

Uses in special populations

- *Elderly/pregnancy/lactation*: see Phenobarbital, pp. 555–8.
- *Lactation*: unmetabolized primidone can also accumulate in breastfed infants to levels similar to maternal plasma levels.

Efficacy

- *Epilepsy*: there are few studies on the clinical efficacy of primidone in the management of epilepsy. One recent RCT looked at the benefits of using primidone or valproate as an add-on in carbamazepine-unresponsive patients with focal-onset epilepsy. It demonstrated quite clearly that 15% more patients could expect a reduction in their seizure frequency by at least 50% with valproate, compared to primidone.
- *ET*: a recent systematic review identified six small RCTs that assessed the use of primidone for ET. The average reduction in tremor was 59·9%. About half of patients with ET respond to primidone, but this response is moderate in most (50% reduction in tremor amplitude and improvement in rating scales), and this may not be sufficient for patients with advanced ET.

Dosing and monitoring

Dosing

- *Epilepsy*: start treatment at 125mg once at night. Then increase by 125mg every 3 days, until 500mg/day is reached in two divided doses. Then the dose can be increased by 250mg, in divided doses every 3 days. The normal maintenance dose is 0.75–1.5g daily.
- *ET*: start treatment at 50mg/day at bedtime. This can be titrated up to a usual maintenance dose of 250mg/day in 1–2 divided doses gradually over the course of 2–3 weeks, as tolerated/required. Doses of up to 750mg/day may be beneficial.

Routine monitoring Monitoring of FBC and LFTs are usually not necessary. Consider vitamin D supplementation and DEXA scans in patients at risk of osteoporosis.

Therapeutic drug monitoring This can be performed by measuring phenobarbital levels. Optimum seizure control, when used as monotherapy, occurs at plasma phenobarbital levels of 10–40mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

The oral bioavailability of primidone is >90%. The effect of food co-ingestion on phenobarbital bioavailability is not known. T_{max} is 2–4h in adults. Protein binding is 10%. Primidone reaches steady state in 2–4 days, phenobarbital in 15–30 days. Primidone is hepatically metabolized to phenobarbital and PEMA. Both are active metabolites, although the anti-convulsant potency of PEMA is markedly less than that of phenobarbital. Phenobarbital undergoes autoinduction, and hence a dosing increase may be required when plasma levels have reached steady state. The majority of

primidone and its metabolites are renally excreted. During monotherapy, ~65% is excreted unchanged in the urine; with enzyme-inducing AEDs, this is reduced to ~40%. As with phenobarbital, the plasma half-life varies, depending on co-administration of enzyme-inducing medication and age. The half-life in adults without co-administration of enzyme-inducing drugs is 7–22h; with these drugs, it is 3–12h.

Interactions See Table A.102.

Table A.102 Interactions of primidone

Medications which alter primidone plasma levels	Medications whose plasma levels are altered by primidone
Levels decreased: acetazolamide, carbamazepine, isoniazid, and phenytoin (carbamazepine and phenytoin increase phenobarbital levels) **Levels increased:** clobazam, ethosuximide, and stiripentol	**Levels decreased:** carbamazepine, clonazepam, ethosuximide, lamotrigine, rufinamide, stiripentol, tiagabine, topiramate, valproate, and zonisamide

References

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Mattson RH, Cramer JA, Collins JF, *et al*. Comparison of carbamazepine, phenobarbital, phenytoin and primidone in partial and secondarily generalized tonic-clonic seizures. *N Engl J Med* 1985;**313**(3):145–51.

Sun MZ, Deckers CL, Liu YX, *et al*. Comparison of add-on valproate and primidone in carbamazepine-unresponsive patients with partial epilepsy. *Seizure* 2009;**18**(2):90–3.

Zesiewicz T, Elble R, Louis E, *et al*. Practice parameter: therapies for essential tremor report of the quality standards subcommittee of the American Academy of Neurology. *Neurology* 2005;**64**(12):2008–20.

Procarbazine

Procarbazine was first licensed for use in the late 1960s. It has multiple mechanisms of action, including alkylation. It rapidly diffuses across the blood–brain barrier and is commonly used as part of the PCV (procarbazine, lomustine, and vincristine) regimen for brain tumours. Its myelosuppressive effects are milder than lomustine, although it is limited by both pharmacokinetic and pharmacodynamic drug interactions.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- *Hodgkin's lymphoma*: procarbazine is licensed for use in the management of Hodgkin's lymphoma (UK: in individuals aged 2 years and above; USA: in individuals of all ages), as part of a chemotherapy protocol.

Off-licence uses

- CNS tumours, non-Hodgkin's lymphomas, and PCNSL.

Presentation

- *Trade names*: Matulane®. Generics are available.
- *Formulations*: procarbazine is available as a 50mg capsule.

Mechanism of action

The precise mechanism of action is unclear. Procarbazine may act by inhibition of DNA, protein, and RNA synthesis via inhibiting transmethylation of methyl groups of methionine to tRNA. Procarbazine may also have a direct action on DNA synthesis via auto-oxidation and generation of hydrogen peroxide which disrupts the activity of DNA-bound proteins.

Toxicity and side effects

- *Common—cardiovascular*: hypotension, syncope, and tachycardia. *Dermatological*: alopecia, dermatitis, herpes, hyperpigmentation, and urticaria. *Endocrine*: gynaecomastia. *Gastrointestinal*: anorexia, nausea, and vomiting are very common. Constipation, diarrhoea, hepatic dysfunction, and stomatitis can occur. *Haematological*: bone marrow suppression, resulting in anaemia, leucopenia, and thrombocytopenia, are very common but are usually reversible and rarely require cessation of treatment.
- *Serious—endocrine*: irreversible azoospermia and ovarian failure have been reported. *Oncology*: secondary malignancies, such as acute myeloid leukaemia and lung cancer, have been reported with the use of procarbazine-containing chemotherapy regimens.

Contraindications

- *Absolute*: hypersensitivity to procarbazine or one of the formulation components and pre-existing severe bone marrow suppression. Avoid in severe hepatic and renal impairment.
- *Relative*: use with caution in cardiovascular and cerebrovascular disease, epilepsy, and phaeochromocytoma due to MAOI activity. Patients should also be advised to avoid tyramine-containing foods/drinks for the same reason. Caution in hepatic and renal impairment.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function, and may benefit from lower dosing regimens.
- *Pregnancy*: human studies have demonstrated teratogenicity in patients taking procarbazine as part of a multi-agent regimen. Animal studies have confirmed that procarbazine alone is associated with fetal malformations. Women of childbearing age should be offered contraception and advised to avoid becoming pregnant.
- *Lactation*: procarbazine levels within breast milk is unknown. Mothers taking procarbazine should avoid breastfeeding.

Efficacy

Procarbazine is commonly used within the context of the PCV chemotherapy regimen. The regimen is most useful in chemotherapy-sensitive tumours, such as anaplastic oligodendroglioma, where studies have shown overall survival is increased from 30.6 to 42.3 months when PCV was given, in addition to radiotherapy, vs radiotherapy alone. For further discussion, see Lomustine, pp. 503–5.

Dosing and monitoring

Dosing

The dosage of procarbazine varies, depending on the BSA, level of bone marrow dysfunction, clinical indication, local protocols, and other adjuvants used in the chemotherapy regimen. Readers are advised to follow local guidelines.

For the treatment of brain tumours, procarbazine is usually given in 4- to 6-weekly cycles as part of a regime, e.g. PCV. A typical regimen is 75mg/m^2 on days 8–21 in four cycles, lasting 6 weeks each.

Routine monitoring Prior to initiation of treatment, FBC, and renal and liver function should be assessed. Weekly FBC is recommended for at least 6 weeks, and the treatment should be suspended temporarily if the WCC falls below 3000 cells/mm^3 or platelets fall below 80 000/mm^3. Liver and renal function should be assessed regularly throughout treatment.

Pharmacokinetics and interactions

Pharmacokinetics

Procarbazine has good oral bioavailability and is rapidly absorbed, reaching peak plasma concentrations 12.5min post-dose. There is good diffusion and distribution into the CSF. Procarbazine is rapidly broken down into its major metabolite azo-procarbazine, most likely by auto-hydrolysis. The half-life of procarbazine is 9.2min. The specific metabolism of the azo-derivative is unclear; there are likely two main subsequent metabolites hydrazine and *N*-isopropylterephalamic acid, which are metabolized by a combination of hepatic and renal processes. Both are predominantly excreted in the urine.

Interactions See Table A.103.

Table A.103 Interactions of procarbazine

Medications whose plasma levels are altered by procarbazine	Pharmacodynamic interactions
Levels decreased: phenytoin and cardiac glycosides	**With alcohol:** disulfiram-like reaction **With cytotoxics and clozapine:** may potentiate myelosuppressive effects **With amphetamine derivatives, SSRIs, SNRIs, noradrenaline–dopamine reuptake inhibitors (NDRIs), TCAs, anaesthetics containing adrenaline, and tyramine-containing foods:** risk of hypertensive crisis secondary to MAOI effect **With enzyme-inducing anticonvulsants:** predispose to procarbazine hypersensitivity reactions

References

Cairncross G, Berkey B, Shaw E, *et al*. Phase III Trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. *J Clin Oncol* 2006;**24**(18):2707–14.

Van den Bent MJ, Brandes AA, Taphorn MJ, *et al*. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol* 2013;**31**(3):344–50.

Van den Bent MJ, Carpentier AF, Brandes AA, *et al*. Adjuvant procarbazine, lomustine and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomised EORTC phase III trial. *J Clin Oncol* 2006;**24**(18):2715–22.

Propranolol

Propranolol, a non-selective β-blocker, has been used in the management of migraine and ET since the 1960s. It is a relatively safe drug, with mainly cardiovascular and gastrointestinal side effects.

Uses

Licensed uses

In the UK/USA

- *Migraine*: propranolol is licensed for use in migraine prophylaxis in individuals aged 18 years and older.
- *ET*: propranolol is licensed for the management of ET in individuals aged 18 years and older.

Off-licence uses

- None.

Presentation

- *Trade names*: Angilol®, Half-Inderal LA®, Inderal LA®, InnoPran XL®, Syprol®. Generics are available.
- *Formulations*: propranolol is available as a modified-release capsule, a modified-release tablet, an oral solution, and a standard tablet. Modified-release capsule: 80mg and 160mg. Modified-release tablet: 80mg and 160mg. Oral solution: 5mg/5mL, 10mg/5mL, 40mg/5mL, and 50mg/5mL. Standard tablet: 10mg, 40mg, 80mg, and 160mg.

Mechanism of action

Propranolol is a non-selective β-adrenoceptor antagonist, and its precise mechanism of action in ET and migraine prophylaxis is not fully understood. In ET, its effects are likely mediated, at least in part, by inhibition of peripheral β-adrenergic receptors, while, in migraine, it is postulated that β1-receptor blockade may modulate cerebral vascular tone. Propranolol may also reduce the frequency of migraine through interaction with serotonin pathways.

Toxicity and side effects

The commonest limiting side effect of propranolol is lethargy.

- *Common—cardiovascular*: bradycardia, coldness of extremities, hypotension. *Dermatological*: exacerbation of psoriasis. *Endocrine*: dyslipidaemia, hyperglycaemia, hypoglycaemia, hyperkalaemia. *Gastrointestinal*: diarrhoea, nausea, vomiting. *Neurological*: dizziness, insomnia, lethargy. *Psychiatric*: depression.
- *Serious—cardiovascular*: AV block, heart failure. *Haematological*: agranulocytosis. *Respiratory*: bronchospasm, pneumonitis, pulmonary fibrosis.

Contraindications

- *Absolute*: asthma, cardiogenic shock, COPD, hypersensitivity, hypotension, second- and third-degree heart block, severe sinus bradycardia, severe peripheral vascular disease, sick sinus syndrome, uncontrolled heart failure.

- *Relative*: depression, diabetes. In severe hepatic impairment, the bioavailability of propranolol is increased, and dose reduction is advised. A lower starting dose of 20mg bd to tds is recommended, with close monitoring of the heart rate with dose increases. Mild/moderate hepatic impairment and renal impairment do not usually require reduced doses, but patients with severe renal impairment should have their heart rate closely monitored.

Uses in special populations

- *Elderly*: a lower dose may be used to initiate therapy, as renal, hepatic, and cardiac diseases are commoner in this group and increase the risk of toxicity.
- *Pregnancy*: beta-blockers can restrict fetal growth, and cause neonatal bradycardia and hypoglycaemia if used at the time of labour. Propranolol should only be used in pregnancy if the benefit outweighs the risk.
- *Lactation*: although present in breast milk, there have been no reported adverse effects, so it is deemed safe to use.

Efficacy

- *ET*: a recent systematic review highlighted 13 double-blind, placebo-controlled studies. The average cohort size was 18 (9–33). Average study duration was 2.9 weeks (0–8 weeks). Tremor was shown to improve on average by 54%, as measured by accelerometry. There have been no long-term studies of propranolol use in ET, although tolerance is believed to develop in 15%.
- *Migraine*: a Cochrane review of propranolol in the prophylaxis of migraine looked at 58 studies with a total of 5072 participants. The review found that propranolol was significantly superior to placebo at reducing headache frequency but that patients in the propranolol group were more likely to experience adverse effects. Propranolol was found to be almost twice as effective as placebo (relative risk of response to treatment 1.94, 95% CI 1.61–2.35).

Dosing and monitoring

Dosing

Start treatment at 40mg bd to tds. This can be increased by 40mg every 2–3 weeks, as required/tolerated. The usual maintenance dose for ET is 120–320mg/day and for migraine is 80–160mg/day.

Routine monitoring Patients should have their heart rate assessed regularly and ECG monitoring if they are at risk of bradycardia.

Pharmacokinetics and interactions

Pharmacokinetics

The bioavailability of propranolol is 25%, due to extensive first-pass metabolism. Peak plasma concentrations occur at 1–4h post-dose. Co-ingestion with food increases the bioavailability but to a variable extent. The half-life is 3–6h. About 90% of the drug is protein-bound. Propranolol comprises two enantiomers R(+) and S(−). R(+) tends to bind to albumin, while S(−) binds

to α1 glycoprotein. Hepatic aromatic hydroxylation and N-dealkylation are believed to be the main routes of metabolism. The cytochrome P450 enzymes CYP2D6 and CYP1A2 are involved. The main metabolite 4-hydroxypropranolol is active. The metabolites are mainly renally excreted, with only 1–4% appearing in the faeces.

Interactions See Table A.104.

Table A.104 Interactions of propranolol

Medications which alter propranolol plasma levels	Medications whose plasma levels are altered by propranolol	Pharmacodynamic interactions
Levels increased: chlorpromazine, cimetidine, dronaderone, fluvoxamine **Levels decreased:** levothyroxine, phenobarbital, rifampicin	**Levels increased:** chlorpromazine, imipramine, rizatriptan	**With diltiazem and verapamil:** severe hypotension and AV node block **With adrenaline, dobutamine, and NA:** risk of severe hypertension and bradycardia **With antihypertensives:** increased risk of hypotension **With amiodarone and other anti-arrhythmics, including lidocaine:** increased rick of myocardial depression

References

Linde K, Rossnagel K. Propranolol for migraine prophylaxis. *Cochrane Database Syst Rev* 2004;**2**:CD003225.

Zesiewicz T, Elble R, Louis E, *et al*. Practice parameter: therapies for essential tremor report of the quality standards subcommittee of the American Academy of Neurology. *Neurology* 2005;**64**(12):2008–20.

Quinine

Quinine is a plant alkaloid originally obtained from the bark of the cinchona tree of South America. It is an optical isomer of the antiarrhythmic agent quinidine. Uncontrolled trials from over 70 years ago first reported its benefits as a treatment for cramps.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- There are no licensed neurological uses.

Off-licence uses

- Muscle cramps in adult patients.

Presentation

- *Trade name*: Qualaquin®. Generics are available.
- *Formulations*: quinine is available as a solution for IV injection and as an oral tablet. Solution for IV injection: 300mg/mL. Tablet: 200mg and 300mg.

Mechanism of action

Muscle cramps are painful, involuntary contractions usually associated with electrical activity. Their aetiology remains unknown; thus, any pharmacological therapy is empirical in nature. Hypotheses include hyperexcitable motor nerve terminals and spinal disinhibition, resulting in hyperactivity of motor neurons. Quinine is thought to increase the refractory period of the muscle, therefore reducing its response to repetitive stimulation.

Toxicity and side effects

- *Common—cardiovascular*: QT prolongation, syncope. *Dermatological*: angio-oedema, flushed skin, rash. *Endocrine*: hypoglycaemia (particularly after IV administration). *Gastrointestinal*: abdominal pain, nausea, vomiting. *Neurological*: ataxia, headache, tinnitus, vertigo, weakness. *Ophthalmological*: blurred vision, photosensitivity. *Respiratory*: exacerbation of asthma, dyspnoea.
- *Serious—cardiovascular*: cardiac arrest, ventricular arrhythmia. *Haematological*: agranulocytosis, aplastic anaemia, disseminated intravascular coagulation (DIC), haemolytic uraemic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP). *Neurological*: blindness. *Renal*: acute kidney injury.

Contraindications

- *Absolute*: hypersensitivity to quinine, mefloquine, or quinidine (cross-sensitivity reported); MG (as quinine has neuromuscular-blocking properties); optic neuritis (quinine may exacerbate this); glucose-6-phosphate dehydrogenase (G6PD) deficiency (may cause haemolysis); tinnitus; haemoglobinuria.
- *Relative*: dose reduction and frequency advised in chronic renal failure. Dose adjustment is not required in hepatic impairment.

Uses in special populations

- *Elderly*: the half-life is doubled in the elderly, due, in part, to an age-related decline in renal function. The dose should be reduced to avoid accumulation and toxicity.
- *Pregnancy*: nearly half of pregnant women may suffer from leg cramps. Quinine is contraindicated due to its teratogenicity in the first trimester, and non-drug measures are preferred (stretching and massage of the affected muscle).
- *Lactation*: quinine enters breast milk and should be used with caution in breastfeeding mothers.

Efficacy

A recent meta-analysis of 23 controlled trials has shown that quinine significantly reduces cramp number (by 28%), intensity (by 10%), and days (by 20%), compared to placebo. However, a significant number (+3% risk difference, 95% CI 0–6%) of people suffered from minor adverse effects with quinine, compared with placebo. In 2010, the FDA issued cautions against the use of quinine for this indication, due to its extensive side effect profile and uncertainty over its efficacy. The MHRA echoed this statement for the UK, although quinine use may still be considered if leg cramps are severe or cause regular sleep disruption. There is no evidence to support the use of quinine or any other medication to control cramps in ALS.

Dosing and monitoring

Dosing

Doses of 200–300mg nightly for 4–6 weeks, and continue for 3 months if symptomatic relief. Doses up to 500mg have been used.

Monitoring Medication review is recommended 3 months after initiation to assess efficacy of treatment. During treatment course, FBC, LFTs, blood glucose, and ECG should be regularly monitored. Ophthalmological review should be considered if visual symptoms occur.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is 76–88%, with no effect of food co-ingestion. T_{max} occurs at 2–4h. Between 69% and 92% of the drug is protein-bound. It undergoes hepatic metabolism via CYP450 enzymes to several metabolites, with one major metabolite (3-hydroxyquinine) being pharmacologically active, but less so than the parent drug. The metabolites are predominantly excreted by the renal tract; 20% of the ingested drug is excreted unchanged in the urine.

Interactions See Table A.105.

Table A.105 Interactions of quinine

Medications which alter quinine plasma levels	Medications whose plasma levels are altered by quinine	Pharmacodynamic interactions
Levels decreased: rifampicin **Levels increased:** atazanavir,cimetidine, darunavir, fosamprenavir, indinavir, ritonavir, tipranavir, warfarin	**Levels increased:** amantadine, digoxin, flecainide, suxamethonium	**With amiodarone, halofantrine, haloperidol, droperidol, mefloquine, moxifloxacin, pimozide, saquinavir, agents which prolong the QT interval:** increased risk of ventricular arrhythmias

References

Connolly PS, Shirley EA, Wasson JH, *et al*. Treatment of nocturnal leg cramps. A crossover trial of quinine vs vitamin E. *Arch Int Med* 1992;**152**(9):1877–80.

El-Tawil S, Al Musa T, Valli H, *et al*. Quinine for muscle cramps. *Cochrane Database Syst Rev* 2010;**12**:CD005044.

Retigabine (ezogabine)

Retigabine was first marketed in the UK as an AED in 2010. In the UK, it is known as retigabine, and in the USA as ezogabine. Its use is currently restricted to individuals with refractory focal-onset epilepsy; however, animal models of seizures have shown that retigabine is effective across a broad spectrum of seizure types, including tonic–clonic and absence seizures. This suggests that retigabine has the potential for wider use, following the appropriate clinical trials.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- *Epilepsy*: retigabine is licensed as an adjunct for the treatment of focal-onset seizures in individuals 18 years of age and older.

Off-licence uses

- None.

Presentation

- *Trade names*: Potiga® and Trobalt®. Generics are not available.
- *Formulations*: retigabine is available as a film-coated tablet at doses of 50mg, 100mg, 200mg, 300mg, and 400mg.

Mechanism of action

In vitro studies have demonstrated that the main antiepileptic action of retigabine is mediated by the opening of neuronal potassium channels Kv7.2 and Kv7.3. This stabilizes neuronal cell membranes and prevents the transmission of epileptic activity.

Toxicity and side effects

- *Common—cardiovascular*: peripheral oedema. High-dose retigabine has been shown to prolong the QT interval by up to 6.7ms in individuals on 1200mg/day. *Gastrointestinal*: constipation, dry mouth, dyspepsia, nausea, and weight gain (~2–3% can occur at higher doses secondary to increased appetite). *Neurological*: dizziness and fatigue are the commonest side effects. Amnesia, confusion, dysphasia, impaired attention, balance, and coordination, myoclonus, tremor, and vertigo are common. *Ophthalmological*: blurred and double vision. *Psychiatric*: anxiety. *Urological*: dysuria, haematuria, and urinary hesitation.
- *Serious—psychiatric*: reports of psychosis and suicidal ideation.

Contraindications

- *Absolute*: hypersensitivity to retigabine or its excipients.
- *Relative*: patients with known QT prolongation or at risk of QT prolongation due to cardiac failure, co-prescribed medications, ventricular hypertrophy, or hypomagnesaemia and other electrolyte abnormalities should be monitored carefully. In moderate to severe hepatic impairment, the starting dose should be halved and then

increased by 50mg every week up to a maximum of 600mg daily (450mg in the over 65 year olds). No dosage change is required for mild hepatic impairment. Retigabine is mainly eliminated by the renal system. Mild renal impairment with an eGFR >50mL/min/1.73m^2 requires no changes in dose. At an eGFR <50mL/min/1.73m^2, the starting dose should be halved and increased by 50mg in weekly intervals to a maximum of 600mg (450mg in the >65 year olds).

Uses in special populations

- *Elderly*: there are only limited data about use in the elderly; the manufacturer recommends a reduction in dosing, so that the initial dose is 150mg daily in three divided doses, and this can be increased by up to 150mg weekly, according to response. The recommended maximum is 900mg daily in three divided doses.
- *Pregnancy*: evidence in animal studies suggests there may be some teratogenic effects. There have been no trials in humans. The manufacturer recommends avoiding use in pregnancy.
- *Lactation*: it is not known whether retigabine is present in human breast milk, although it has been identified in rodent breast milk. If used, infants should be monitored for potential side effects and switched to an alternative feeding regimen if these are identified.

Efficacy

There have been three phase 3 clinical trials looking at the efficacy and safety of retigabine in patients with focal-onset seizures. Recent meta-analyses and systematic reviews have demonstrated the effectiveness of retigabine in the setting of refractory epilepsy.

Dosing and monitoring

Dosing

- Age >18 years old: start treatment at up to 300mg daily in three divided doses. This can be increased, depending on the response, by up to 150mg weekly. Normal maintenance doses are 0.6–1.2g daily in three divided doses.

Routine monitoring Patients at risk of QT prolongation should have an ECG prior to starting treatment and a further ECG when the maintenance dose has been achieved.

Therapeutic drug monitoring There are no data relating plasma retigabine levels with that of seizure suppression or adverse effects.

Pharmacokinetics and interactions

Pharmacokinetics

The oral bioavailability of retigabine is ~60%; food co-ingestion does not significantly change bioavailability or the rate of absorption. T_{max} is 0.5–2h. Retigabine is 80% plasma protein-bound. It undergoes extensive hepatic metabolism to inactive metabolites, both an *N*-glucuronide and an *N*-acetyl metabolite which is then glucuronidated. There is no interaction with the cytochrome P450 system. ~84% of the drug is eliminated by the renal

system; a third of this is unchanged drug. The rest is excreted in the faeces. The plasma half-life is 6–10h.

Interactions See Table A.106.

Table A.106 Interactions of retigabine (ezogabine)

Medications which alter retigabine plasma levels	Medications whose plasma levels are altered by retigabine	Pharmacodynamic interactions
Levels decreased: carbamazepine and phenytoin **Levels increased:** lamotrigine and phenobarbital	**Levels increased:** digoxin, phenobarbital, and thiopental sodium	**With alcohol:** may increase the chance of blurred vision

References

Gao L, Xia L, Zhao FL, Li SC. Clinical efficacy and safety of the newer antiepileptic drugs as adjunctive treatment in adults with refractory partial-onset epilepsy: a meta-analysis of randomized placebo-controlled trials. *Epilepsy Res* 2013;**103**(1):31–44.

Martyn-St James M, Glanville J, McCool R, *et al*. The efficacy and safety of retigabine and other adjunctive treatments for refractory partial epilepsy: a systematic review and indirect comparison. *Seizure* 2012;**21**(9):665–78.

Yamada M, Welty TE. Ezogabine: an evaluation of its efficacy and safety as adjunctive therapy for partial-onset seizures in adults. *Ann Pharmacother* 2012;**46**(10):1358–67.

Riluzole

Riluzole was originally developed in the 1950s as a centrally acting muscle relaxant and was later employed for its anticonvulsant, sedative, and neuroprotective features. Riluzole was approved for use in MND in the 1990s.

Uses

Licensed uses

In the UK/USA

- MND: riluzole is licensed to extend life in patients with ALS in individuals aged 18 years and older.

Off-licence uses

- Other phenotypic variants of MND, HD, and PD.

Presentation

- *Trade names*: Rilutek®. Generic forms are available.
- *Formulations*: riluzole is available as a 50mg tablet.

Mechanism of action

The mechanism of action of riluzole is not fully understood. Among its complex effects are inhibition of the presynaptic release of glutamate, as well as sodium, calcium, and potassium currents.

Toxicity and side effects

- *Common—cardiovascular*: hypertension, peripheral oedema, tachycardia. *Gastrointestinal*: abdominal pain, diarrhoea, nausea, vomiting. *Neurological*: dizziness, headache, somnolence, paraesthesiae, vertigo, weakness.
- *Serious—gastrointestinal*: hepatitis, pancreatitis. *Respiratory*: interstitial lung disease.

Contraindications

- *Absolute*: hypersensitivity to riluzole, hepatic disease, or baseline ALT >3x ULN.
- *Relative*: abnormal LFTs. No dose adjustments required in renal impairment.

Uses in special populations

- *Elderly*: the elderly experience an age-related deterioration in hepatic and renal function, and hence caution is required.
- *Pregnancy*: riluzole is contraindicated, due to embryo toxicity in animal models.
- *Lactation*: it is not known whether riluzole is excreted in human breast milk; avoidance is advised.

Efficacy

Riluzole is the only drug to influence survival in ALS, as shown by four RCTs to date. The drug improves the probability of surviving 1 year by 9%, and median survival is increased by 3 months (17.7 months vs 14.9 months with placebo). It has very little, if any, effect on secondary outcomes measures,

e.g. muscle strength. Studies looking at use in late stage disease (average vital capacity <60%) have not shown a significant improvement in survival time or muscle strength.

Dosing and monitoring

Dosing

Commence and continue at 50mg bd, an hour before, or 2h after, food.

Monitoring Riluzole should be prescribed with care in those with premorbidly abnormal liver chemistries. Regular monitoring of hepatic function is recommended (monthly for 3 months, then 3-monthly for a further 9 months, annually thereafter). The manufacturer advises discontinuation of riluzole if ALT levels are >5 times the upper limit of normal or if jaundice develops. Clinicians should have a low threshold for chest radiography if dry cough or dyspnoea develops, due to risk of interstitial lung disease.

Pharmacokinetics and interactions

Pharmacokinetics

Riluzole has a bioavailability of 60%, which is affected by food intake. Fatty meals reduce peak blood levels by 45%. It is 96% bound to plasma proteins and has an elimination half-life of 12h. With multiple-dose administration, a steady state is reached in <5 days. It undergoes hepatic metabolism by cytochrome P4501A2; therefore, concurrent usage of other inhibitors of CYP1A2, such as caffeine and cigarette smoking, should be avoided. Excretion is predominantly via the urine (85% as metabolites, 2% as unchanged drug) and faeces (5%).

Interactions See Table A.107.

Table A.107 Interactions of riluzole

Medications which alter riluzole plasma levels
Levels decreased: cigarettes, charcoal-broiled food, omeprazole, and rifampicin
Levels increased: amitriptyline, caffeine, clomipramine, diclofenac, diazepam, fluvoxamine, imipramine, nicergoline, phenacetin, quinolones, theophylline

References

Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev* 2012;**3**:CD001447.

National Institute for Health and Care Excellence (2001). *Guidance on the use of Riluzole (Rilutek) for the treatment of Motor Neurone Disease*. NICE technology appraisal guidance TA20. Available at: https://www.nice.org.uk/guidance/ta20.

Rituximab

Rituximab is a chimeric monoclonal antibody. It was initially developed in the 1990s as a treatment for non-Hodgkin's lymphoma. It was shown to be effective in rheumatoid arthritis in 2004 and is now used in a wide range of autoimmune neurological diseases.

Uses

Licensed uses

In the UK/USA

- Rituximab is licensed for the treatment of granulomatosis with polyangiitis (Wegener's granulomatosis) and microscopic polyangiitis with corticosteroids in individuals aged 18 years and older.

Off-licence uses

- CANOMAD.
- IgM paraproteinaemic neuropathy with anti-MAG antibodies.
- Primary CNS vasculitis (refractory cases, chronic).
- LEMS (resistant cases, chronic).
- MG (refractory cases, chronic).
- Neurolupus.
- NMO (first-line, chronic).
- PM/DM (refractory cases, chronic).
- Sjögren's syndrome.
- Stiff person syndrome (refractory cases).

Presentation

- *Trade names*: MabThera® and Rituxan®. Generics are not available.
- *Formulations*: rituximab is available as a concentrate for IV infusion and a solution for SC injection. Concentrate for IV infusion (10mg/mL): 100mg and 500mg. Solution for SC infusion (1400mg/11.7mL): 1400mg.

Mechanism of action

Rituximab is a chimeric mouse/human monoclonal antibody, which targets the CD20 antigen located on pre-B and mature B cell lymphocytes. It depletes B cells by promoting apoptosis and mediating cell lysis through cell-mediated cytotoxicity.

Toxicity and side effects

- *Common—dermatological*: alopecia. *Endocrine*: hypercholesterolaemia. *Gastrointestinal*: abdominal pain, diarrhoea, dyspepsia, gastroenteritis, and stomatitis. *Musculoskeletal*: arthralgia and myalgia. *Neurological*: dizziness, headache, and paraesthesiae. *Psychiatric*: anxiety and depression. *Respiratory*: respiratory tract infections.
- *Serious—cardiovascular*: congestive heart failure and MI. *Dermatological*: Stevens–Johnson syndrome and toxic epidermal necrolysis. *Haematological*: neutropenia. *Immunological*: hypersensitivity (including anaphylaxis), increased risk of infections, and infusion-related reactions. *Neurological*: PML.

Contraindications

- *Absolute*: hypersensitivity, active/severe infections, immunosuppression, severe heart failure, and uncontrolled cardiac disease.
- *Relative*: there are limited data on the use of rituximab in renal or hepatic impairment, but dose reductions are not required.

Use in special populations

- *Elderly*: no safety studies have specifically been conducted in this group. No dose reductions are required.
- *Pregnancy*: IgG immunoglobulins cross the placenta, and treatment should therefore be avoided in pregnancy. Contraception is advised during, and for 12 months following, treatment.
- *Lactation*: it is not clear whether rituximab is excreted in breast milk. Breastfeeding should be avoided during, and for 12 months following, treatment.

Efficacy

See relevant conditions in Chapter 6, Inflammatory disorders of the central nervous system.

Dosing and monitoring

Dosing

Dosing regimens differ, depending on the indication.

- *NMO*: treatment can be initiated using either two 1g infusions of rituximab at an interval of 2 weeks or 4-weekly 375mg/m^2 of BSA.
- *Wegener's granulomatosis*: a weekly infusion of 375mg/m^2 of BSA each week for 4 weeks. Initial doses should be given at a rate of 50mg/h, and this can be increased at 50mg/h increments every 30min, until a maximum rate of 400mg/h. Further infusions can be started at a rate of 100mg/h and increased at 100mg/h increments every 30min, until a maximum rate of 400mg/h. Concurrent infusions of corticosteroids may be necessary to reduce infusion-related reaction. An antihistamine and analgesia should be given preceding the rituximab infusion.

Monitoring Patients should be screened for hepatitis B (with hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) testing) prior to treatment initiation, and the FBC should be measured before, and at regular intervals during, treatment, given the risk of haematological cytopenias. All patients should be observed for infusion reactions and be given a patient alert card with each infusion. Clinical response to rituximab treatment is ideally assessed at 4–6 months after the first dose.

Pharmacokinetics and interactions

Pharmacokinetics

Immunoglobulins and their complexes are mostly broken down by the reticuloendothelial system. The half-life is ~21 days. The drug remains detectable in the serum at 6 months. B cell recovery begins at ~24 weeks, with normalization of B cell levels usually occurring at 1 year. A minority of patients have prolonged B cell depletion lasting 2 years.

Interactions

Vaccines may be less effective during treatment and should be completed at least 4 weeks prior to therapy. Live vaccination should be avoided during treatment.

Rivaroxaban

Rivaroxaban was first marketed in the UK in 2011. It is an effective oral anticoagulant, which can be used when there is poor INR control, despite compliance with warfarin therapy, or to patients who are allergic to, or unable to tolerate, warfarin.

Uses

Licensed uses

In the UK/USA

Rivaroxaban is licensed for the prophylaxis of stroke and systemic embolism in patients with non-valvular AF in individuals aged 18 years or older. In the UK, patients need to score at least 1 point on the CHADS2 VASc score.

Off-licence uses

- None.

Presentation

- *Trade names*: Xarelto®. Generic forms are not available.
- *Formulations*: rivaroxaban is available as a hard capsule in 10mg, 15mg, and 20mg doses.

Mechanism of action

Rivaroxaban is an oxazolidinone derivative optimized for inhibiting both free factor Xa and factor Xa bound in the prothrombinase complex. It is a highly selective direct factor Xa inhibitor, with oral bioavailability and rapid onset of action. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathways of the blood coagulation cascade, inhibiting both thrombin formation and the development of thrombi.

Toxicity and side effects

- *Common—cardiovascular*: hypotension. *Dermatological*: pruritus, rash. *Gastrointestinal*: abdominal pain, constipation, diarrhoea, dyspepsia, nausea, vomiting. *Haematological*: anaemia. *Musculoskeletal*: pain in extremities. *Neurological*: headaches.
- *Serious—haematological*: haemorrhage. *Immunological*: allergic reaction. *Neurological*: ICH.

Contraindications

- *Absolute*: hypersensitivity to rivaroxaban or its excipients, active significant bleeding, a condition predisposing patients to bleeding, e.g. recent intracranial haemorrhage, concomitant treatment with other anticoagulants, hepatic disease with coagulopathy and high bleeding risk, including Child–Pugh B and C cirrhotic patients, metallic heart valves. Severe renal impairment (CrCl <15mL/min).
- *Relative*: in moderate renal impairment, reduce the dose to 15mg od (CrCl 15–49mL/min).

Uses in special populations

- *Elderly*: no dose adjustment is necessary in the elderly population; however, the elderly population experiences an age-related decline in renal and hepatic function; hence these parameters should be regularly monitored.

- *Pregnancy*: toxicity has been demonstrated in animal studies, and thus rivaroxaban should be avoided in pregnancy.
- *Lactation*: animal studies have demonstrated the presence of rivaroxaban in breast milk. Hence, it should not be used by nursing mothers.

Efficacy

In a double-blind RCT (ROCKET AF), rivaroxaban was shown to be non-inferior to warfarin for the primary endpoint of stroke or systemic embolism in patients with non-valvular AF who were at moderate to high risk of stroke (hazard ratio 0.88; 95% CI 0.74–1.03; p <0.001). Intracranial and fatal bleeding was significantly less frequent in the rivaroxaban group (0.5% vs 0.7%, $p = 0.02$ for intracranial, and 0.2% vs 0.5%, $p = 0.03$ for fatal bleeding for rivoroxaban vs warfarin).

Dosing and monitoring

Dosing

The recommended daily dose for prevention of stroke in non-valvular AF is 20mg taken od.

Monitoring There is no need for routine monitoring of coagulation parameters during treatment with rivaroxaban. However, if clinically indicated, rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests. Monitor renal function at least annually.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is 80–100% for 10mg doses, and 66% for 20mg doses. T_{max} occurs at 2–4h. Food co-ingestion increases bioavailability at the 20mg dose. Two-thirds of rivaroxaban is metabolized hepatically via CYP3A4, CYP2J2, and CYP-independent mechanisms. Metabolites are inactive. Elimination is predominantly renal (66%), with half excreted as metabolites and the rest as unchanged drug. The rest is eliminated as metabolites in the faeces. The terminal half-life is 5–9h and 11–13h in the elderly.

Interactions See Table A.108.

Table A.108 Interactions of rivaroxaban

Medications which alter rivaroxaban plasma levels	Pharmacodynamic interactions
Levels decreased: rifampicin **Levels increased:** HIV protease inhibitors, e.g. indinavir and azole antifungals, e.g. itraconazole and ketoconazole	**With anticoagulants, antiplatelets, NSAIDs:** increased risk of bleeding

Reference

Patel MR, Mahaffey KW, Garg JM, *et al*. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**(10):883–91.

Rufinamide

Rufinamide was first marketed in the UK as an AED in 2007. It is an orphan drug (drug used in rare conditions) that is only licensed for the treatment of LGS. Rufinamide may be particularly useful in individuals prone to atonic/drop attacks. Recent clinical trials have investigated its use in the management of focal-onset seizures; however, the effects in the initial trials were reported as marginal.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- *Epilepsy*: rufinamide is licensed, as an adjunct, for the treatment of seizures associated with LGS in individuals aged 4 years and older.

Off-licence uses

- Focal-onset epilepsy.

Presentation

- *Trade names*: Banzel® and Inovelon®. Generics are not available.
- *Formulations*: rufinamide is available as a film-coated tablet and an oral suspension. Film-coated tablet: 100mg, 200mg, and 400mg. Oral suspension: 40mg/mL. These are bioequivalent.

Mechanism of action

The main mechanism of action of rufinamide is thought to be by blocking voltage-gated sodium channels. This inhibits neuronal activity and hence the spread of cerebral epileptic discharges.

Toxicity and side effects

- *Common—dermatological*: acne and rash. *Endocrine*: oligomenorrhoea. *ENT*: ear infections, epistaxis, and sinusitis. *Gastrointestinal*: nausea and vomiting are the commonest side effects. Abdominal pain, constipation, diarrhoea, dyspepsia, reduced appetite, and weight loss are also common. *Musculoskeletal*: back pain. *Neurological*: neurological side effects are usually dose-dependent, and tolerance develops after a few months. Dizziness, headache, and fatigue are very common side effects. Abnormal coordination, hyperactivity, nystagmus, and tremor are common. *Ophthalmological*: blurred and double vision. *Psychiatric*: anxiety and insomnia. *Respiratory*: influenza-like symptoms and pneumonia.
- *Serious—cardiovascular*: shortening of the QT interval, which may cause arrhythmia in predisposed patients, e.g. those with congenital short QT syndrome. *Immunological*: antiepileptic hypersensitivity syndrome has been reported. *Neurological*: an increase in seizures, and even status epilepticus, can be triggered in some individuals.

Contraindications

- *Absolute*: hypersensitivity to triazole derivatives, rufinamide, or any of its excipients. Rufinamide is also contraindicated in congenital short QT syndrome and severe hepatic impairment.
- *Relative*: studies have shown that the pharmacokinetics of a small dose of rufinamide 400mg are unchanged in severe renal impairment. However, rufinamide is predominantly renally excreted, and hence caution and lower doses are still recommended in renally impaired patients. Rufinamide also undergoes extensive hepatic metabolism; hence use caution in mild to moderate hepatic impairment.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function, and may benefit from lower dosing regimens.
- *Pregnancy*: animal studies have demonstrated teratogenic effects; however, there are as yet no studies in humans. It is unknown if the pharmacokinetics of rufinamide change during pregnancy. Use in pregnancy involves weighing up the potential benefits and side effects.
- *Lactation*: it is not known whether rufinamide is present in human breast milk. If used, infants should be monitored for side effects and switched to an alternative feeding regimen if these are identified.

Efficacy

There has only been one RCT looking at the efficacy of rufinamide in LGS. It showed that, when used as an adjunct in a group of patients aged between 4 and 30 years of age, the median percentage reduction in total seizure frequency was statistically significant (32.7%) with rufinamide vs 11.7% with placebo. Tonic–clonic and tonic–atonic (drop attacks) seizures seemed to be the most responsive seizure types. These findings have been corroborated by further open-label, uncontrolled studies carried out in Europe.

Dosing and monitoring

Dosing

- Age >4 years and with a body weight >30kg: start treatment at 200mg bd. Increase the dose in intervals of 2 or more days by 200mg bd. Titrate to response up to a maximum of 1.2g bd in individuals with a body weight of 50–70kg, and 1.6g bd in individuals with a body weight >70kg. The maximum should be adjusted to 300mg bd, if used in conjunction with valproate.

Routine monitoring Hepatic and renal function should be assessed at baseline and annually thereafter. An ECG should be considered before treatment, in order to identify short QT syndrome.

Therapeutic drug monitoring Optimum seizure control, when used in monotherapy, occurs at plasma concentrations of 30–40mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

The exact oral bioavailability has not been determined. However, it is known to be dose-dependent (i.e. bioavailability reduces at higher doses)

and is increased by food co-ingestion. T_{max} is 6h when taken with food, and 8h in the fasted state. A third of rufinamide is bound to plasma proteins, predominantly albumin. Rufinamide is mainly metabolized by hydrolysis to the inactive metabolite CGP 47292 in the liver. Involvement of the cytochrome P450 system is minor. Autoinduction does not occur. 70% of CGP 47292 is excreted in the urine, along with a small amount (<5%) of unmetabolized drug. The rest is excreted in the faeces. The plasma half-life in adults is 6–10h; this is expected to be longer in females.

Interactions See Table A.109.

Table A.109 Interactions of rufinamide

Medications which alter rufinamide plasma levels	Medications whose plasma levels are altered by rufinamide
Levels decreased: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, and vigabatrin **Levels increased:** valproate	**Levels decreased:** carbamazepine, lamotrigine, and triazolam **Levels increased:** phenobarbital and phenytoin

References

Coppola G, Grosso S, Franzoni E, *et al*. Rufinamide in children and adults with Lennox-Gastaut syndrome: first Italian multicentre experience. *Seizure* 2010;**19**(9):587–91.

Luger G, Glauser T, Krauss G, *et al*. Adjunctive rufinamide in Lennox-Gastaut syndrome: a long-term, open-label extension study. *Acta Neurol Scand* 2010;**122**(3):202–8.

Verrotti A, Loiacono G, Ballone E, *et al*. Efficacy of rufinamide in drug-resistant epilepsy: a meta-analysis. *Pediatr Neurol* 2011;**44**(5):347–9.

Sodium oxybate (γ-hydroxybutyrate)

Sodium oxybate was first marketed in the UK in 2006. It is a CNS depressant used in the management of narcolepsy. It is effective in reducing the incidence of cataplexy and excessive daytime sleepiness in this condition. Its use is limited, to some extent, by its side effect of respiratory depression and its potential as a drug of abuse when used in high doses.

Uses

Licensed uses

In the UK/USA

- *Narcolepsy*: sodium oxybate is licensed for the treatment of narcolepsy with cataplexy (and excessive daytime sleepiness in the USA) in individuals aged 18 years and older.

Off-licence uses

Sodium oxybate has been used off-licence in a wide range of conditions, including alcohol dependence, fibromyalgia, and headache disorders.

Presentation

- *Trade names*: Xyrem®. Generics are not available.
- *Formulations*: sodium oxybate is available as an oral solution in 180mL vials of 500mg/mL concentration.

Mechanism of action

The exact mechanism of action of sodium oxybate is unclear. It is the salt of an endogenous compound γ-hydroxybutyrate, a metabolite of the neurotransmitter GABA. Hence it is believed to act at $GABA_b$ receptors on dopaminergic and noradrenergic neurons. The overall result is a CNS depressant effect. Clinically, this promotes delta-wave sleep, increasing stage 3 and 4 sleep, while reducing the frequency of sleep-onset REM periods.

Toxicity and side effects

The commonest side effects occurring in >10% are dizziness, headache, and nausea. γ-hydroxybutyrate also has well-documented dependence effects when used illicitly, although this is thought to occur at higher doses than when used therapeutically. The presence of a withdrawal syndrome on terminating treatment is also unclear—some patients have reported rebound increases in cataplexy and a syndrome comprising headache, and psychotic and sleep disturbance, although there is no clear evidence of this in clinical trial data.

- *Common—cardiovascular*: hypertension and palpitations. *Dermatological*: hyperhidrosis and rash. *ENT*: nasal congestion and vertigo. *Gastrointestinal*: abdominal pain, anorexia, diarrhoea, nausea, and vomiting. *Musculoskeletal*: arthralgia and myalgia. *Neurological*: dizziness, dysgeusia, fatigue, headache, impaired balance and concentration, paraesthesiae, sedation, sleep paralysis, and tremor are common. *Ophthalmological*: blurred vision. *Psychiatric*: abnormal dreams, confusion, insomnia, mood disorders, and sleepwalking. *Respiratory*: dyspnoea and snoring.

- *Serious—psychiatric*: psychosis and suicidality are uncommon. *Respiratory*: apnoea and respiratory depression, which are commoner in patients with pre-existing sleep-related breathing disorders.

Contraindications

- *Absolute*: concomitant use of sedative hypnotic agents, e.g. alcohol, barbiturates, benzodiazepines, and opiates. Porphyria, previous hypersensitivity reactions to sodium oxybate or its excipients, major depression, and patients with succinic semialdehyde dehydrogenase deficiency.
- *Relative*: patients with cardiovascular disorders such as heart failure and hypertension (due to high sodium load of the formulation), epilepsy (an increase in seizure frequency has been reported), history of drug abuse, and pre-existing respiratory depression. The starting dose should be halved in hepatic impairment, and treatment should be used with caution in patients with renal impairment, due to the high sodium load.

Uses in special populations

- *Elderly*: there are limited trial data of use of sodium oxybate in the elderly. The elderly have an age-related deterioration in their renal and hepatic function, and hence may benefit from lower dosing regimens. Co-prescription of other medications is also more likely in the elderly, and hence the risk of pharmacokinetic and pharmacodynamic interactions, particularly CNS depression, is increased.
- *Pregnancy*: animal studies and data from a small number of pregnant women suggest increased rates of intrauterine death in the first trimester. Teratogenicity has not been reported. Sodium oxybate should be avoided in pregnancy.
- *Lactation*: the presence of sodium oxybate in breast milk is unknown. It should not be used by breastfeeding mothers.

Efficacy

A recent systematic review and meta-analysis of the use of sodium oxybate in narcolepsy–cataplexy patients identified six suitable RCTs. All six trials demonstrated a reduction in cataplexy attacks in a dose-related manner vs placebo. The mean difference was −8.5% (95% CI −15.3 to −1.6) (the commonest dose used was 9g/night). In addition, the study showed that excessive daytime sleepiness was reduced, as measured by the maintenance of wakefulness test, demonstrating a mean difference of 5.18% (95% CI 2.59–7.78).

Dosing and monitoring

Dosing

The initial starting dose should be 4.5g/night. This should be split into two 2.25g doses, taken last thing before sleep and ~3 hours before this. This can be increased in intervals of 1–2 weeks by 1.5g, as required; this increase should be split over the two dosing times. The maximum recommended dose is 9g/night (titration will need to be re-commenced if the medication has not been used for 2 weeks or more).

Routine monitoring Patients with a diagnosis or risk factors for sleep-related breathing disorders should be carefully monitored throughout treatment. Snoring severity scales and nocturnal oximetry can be used to further investigate these patients.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability of sodium oxybate is ~88%. Peak plasma concentrations occur at 0.5–1.25h post-dose. Peak plasma concentration and the time at which it is reached post-dose is reduced by 59% and increased to 0.75–2h, respectively, with co-ingestion of a high-fat meal. Sodium oxybate is <1% protein-bound. Clearance is via biotransformation to carbon dioxide and water by γ-hydroxybutyrate dehydrogenase and the Krebs cycle. No active metabolites have been identified. Less than 5% of unchanged drug is present in the urine. The majority is expired as carbon dioxide. The elimination half-life is 0.5–1h.

Interactions See Table A.110.

Table A.110 Interactions of sodium oxybate

Pharmacodynamic interactions
With antipsychotics, barbiturates, benzodiazepines, opioids, TCAs: increased risk of CNS depression
Sodium oxybate is metabolized by γ-hydroxybutyrate dehydrogenase. Potentially, AEDs, such as sodium valproate, phenytoin, and ethosuximide, whose mechanism of action includes inhibition/stimulation of this enzyme may alter sodium oxybate plasma levels; however, no interaction studies have as yet been conducted.

References

Alshaikh MK, Tricco AC, Tashkandi M, *et al*. Sodium oxybate for narcolepsy with cataplexy: systematic review and meta-analysis. *J Clin Sleep Med* 2012;**8**(4):451–8.

Xyrem International Study Group. Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo-controlled study in 228 patients. *Sleep Med* 2005;**6**(5):415–21.

Temazepam

Temazepam was first marketed in the UK in the 1960s. It is primarily used as a hypnotic in the short-term treatment of insomnia. It is effective at reducing the time to sleep onset, maintaining sleep, and improving sleep quality. However, like with other benzodiazepines and benzodiazepine-like drugs, its use is limited by its potential for addiction and tolerance with longer-term use. It has a relatively short half-life, when compared to other benzodiazepines, which likely reduces the impact of the benzodiazepine side effect profile. It is, however, still associated with behavioural and sedative side effects, particularly in the elderly.

Uses

Licensed uses

In the UK

- *Insomnia*: temazepam is licensed as a short-term treatment of insomnia in instances where it is severe, disabling, or subjecting the individual to extreme distress, in individuals aged >18 years old.

In the USA

- *Insomnia*: temazepam is licensed for the short-term (usually 7–10 days) treatment of insomnia in individuals aged >18 years old.

Off-licence uses

- None.

Presentation

- *Trade names*: Restoril®. Generics are available.
- *Formulations*: temazepam is available as an oral solution and a tablet. Oral solution: 300mL vial (10mg/5mL). Tablet: 10mg and 20mg.

Mechanism of action

See Benzodiazepines, pp. 287–93.

Toxicity and side effects

See Benzodiazepines, pp. 287–93. Rebound insomnia on cessation of treatment can occur.

Contraindications

See Benzodiazepines, pp. 287–93. Temazepam is also contraindicated in acute narrow-angle glaucoma.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function. Side effects, including behavioural changes, confusion, headache, falls, and respiratory depression, are also commoner. They benefit from lower doses, i.e. 5mg. This can be increased to 10–20mg if insomnia is severe.
- *Pregnancy*: the effects of temazepam in pregnancy have yet to be determined. Human studies of other benzodiazepine drugs have demonstrated teratogenic potential. Neonates are at risk of flaccidity,

respiratory depression, and withdrawal if used in the latter half of pregnancy or in labour. Use in pregnancy should be avoided, unless there is a strong indication.
- *Lactation*: temazepam has been found in human breast milk. Breastfeeding should be avoided, while temazepam is being taken, where possible. If taken by nursing mothers, the infant should be monitored for respiratory depression, sedation, and withdrawal (if temazepam is abruptly discontinued).

Efficacy

A randomized, double-blind, placebo-controlled trial published in 1979 compared the action of temazepam 30mg with placebo. The trial showed that temazepam resulted in a statistically significant improvement in sleep induction (p <0.05). The actual time to fall asleep was a mean of 44min with temazepam vs 82min with placebo. Total sleep length and number of nocturnal awakenings were also improved. One meta-analysis comparing the benzodiazepines temazepam, triazolam, and nitrazepam with the benzodiazepine agonists zaleplon, zolpidem, and zopiclone found no significant difference in subjective sleep quality or overall adverse effects between the drug groups. There are no RCTs comparing temazepam at the standard 10mg with the newer Z-drugs.

Dosing and monitoring

Dosing

Start treatment at 10–20mg before sleep. This can be increased to a maximum of 40mg if insomnia is severe. Temazepam should be used for the shortest possible duration, certainly <4 weeks.

Routine monitoring Not usually required. The elderly and those with hepatic impairment should be monitored for confusion.

Pharmacokinetics and interactions

Pharmacokinetics

See Benzodiazepines, pp. 287–93.

Interactions See Benzodiazepines, pp. 287–93.

References

Glass JR, Lanctôt KL, Herrman N, *et al*. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ* 2005;**331**(7526):1169–73.

Heffron WA, Roth P. Double-blind evaluation of the safety and hypnotic efficacy of temazepam in insomniac outpatients. *Br J Clin Pharmacol* 1979;**8**(1):69–72.

Temozolomide

Temozolomide was first licensed for use in the late 1990s. It is a derivative of the alkylating agent dacarbazine. It has proven efficacy in the first-line treatment of glioblastoma and in the treatment of recurrence in other high-grade gliomas. As per most of the chemotherapeutic agents, its use is limited by its side effect profile, particularly myelosuppression.

Uses

Licensed uses

In the UK/USA

- *GBM*: temozolomide is licensed for use with radiotherapy in the treatment of newly diagnosed GBM; it may then be used as monotherapy alone in individuals aged 18 years and older.

In the UK

- *Malignant glioma*: temozolomide is licensed for the treatment of malignant glioma which recurs or progresses after first-line therapy in individuals aged 3 years and older.

In the USA

- *Anaplastic astrocytoma*: temozolomide is licensed for use in the treatment of refractory anaplastic astrocytoma following chemotherapy containing a nitrosourea and procarbazine, in individuals aged 18 years and older.

Off-licence uses

- Other brain tumours, e.g. ependymoma, pituitary tumours.

Presentation

- *Trade names*: Temodal®, Temodar®, Temomedac®, and Temozolomide Hospira®. Generics are available.
- *Formulations*: temozolomide is available as a capsule in 5mg, 20mg, 100mg, 140mg, 180mg, and 250mg doses, and as a powder for IV injection at 100mg/vial.

Mechanism of action

Temozolomide is a prodrug. Its active metabolite monomethyl triazeno imidazole carboxamide (MTIC) is formed at physiological pH and acts as an alkylating agent inhibiting DNA replication.

Toxicity and side effects

- *Common—dermatological*: alopecia, pruritus, and rash. *Endocrine*: adrenal hypercorticism and weight increase. *Gastrointestinal*: abdominal pain, anorexia, and gastrointestinal disturbance are common. *Musculoskeletal*: arthralgia and myalgia. *Respiratory*: PCP is common; hence prophylaxis is required. Viral respiratory tract infections are also common.
- *Serious—haematological*: myelosuppression is common, and this can result in fatal aplastic anaemia. Myelodysplastic syndrome with development of secondary malignancies can also occur.

Contraindications

- *Absolute*: patients with previous hypersensitivity reactions to temozolomide, its excipients, or dacarbazine. Severe myelosuppression—prior to dosing, patients must have a platelet count $>100 \times 10^9$/L and a neutrophil count $>1.5 \times 10^9$/L.
- *Relative*: caution should be taken in patients with severe hepatic or renal impairment.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function, and hence may benefit from lower dosing regimens. There is an increased risk of neutropenia and thrombocytopenia in those aged over 70 years.
- *Pregnancy*: temozolomide is associated with fetal malformations in animal studies. Women of childbearing age should be offered contraception and advised to avoid becoming pregnant. Men should avoid fathering a child during, and for 6 months following, treatment.
- *Lactation*: temozolomide levels within breast milk is unknown. Mothers should be advised to avoid breastfeeding.

Efficacy

An RCT of treatment of newly diagnosed GBM demonstrated a significant increase in 2-year survival from 10.4% with radiotherapy alone to 26.5% with radiotherapy and temozolomide.

For recurrent high-grade gliomas, an RCT showed high-dose temozolomide for 5 days was more effective than low-dose temozolomide for 21 days, while there was no clear benefit when comparing temozolomide with a PCV regimen (the percentages of patients completing 9 months of treatment were 26% vs 13% vs 17%, respectively, for 5 days of high-dose temozolomide, 21 days of low-dose temozolomide, and a typical PCV regimen).

Dosing and monitoring

Dosing

The dosage of temozolomide varies, depending on the BSA, level of bone marrow depression, clinical indication, local protocols, and other adjuvants used in the chemotherapy regimen. Readers are advised to follow local guidelines.

- *Typical regime for high-grade glioma*: 75mg/m^2 for 42 days, alongside focal radiotherapy, followed by six cycles of maintenance chemotherapy using doses of up to 150–200mg/m^2, depending upon toxicity.
- *Typical regime for refractory anaplastic astrocytoma*: an initial dose of 150mg/m^2 daily for 5 days of a 28-day cycle. The dose is adjusted in subsequent cycles, depending on toxicity. The optimum duration of therapy is unknown.

Routine monitoring Prior to initiation of treatment, FBC, and renal and liver function should be assessed. Regular FBC monitoring during treatment is recommended.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability of temozolomide is nearly 100%. Peak plasma concentrations are reached in 0.9h. Oral bioavailability is reduced and T_{max} prolonged by co-administration with food. Temozolomide is ~15% protein-bound. It rapidly crosses the blood–brain barrier and is present in the CSF at ~30% of plasma concentrations. Temozolomide has a short half-life of 1.8h; it is spontaneously hydrolysed at physiological pH to MTIC and temozolomide acid metabolite. MTIC is further metabolized to 5-amino-imidazole-4-carboxamide, an intermediate in DNA synthesis, and methylhydrazine, an alkylating agent. By 7 days, 38% of the temozolomide radioactive dose is recovered, the majority in the urine and 0.8% in the faeces. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC.

Interactions See Table A.111.

Table A.111 Interactions of temozolomide

Medications which alter temozolomide plasma levels	Pharmacodynamic interactions
Levels increased: valproate	**With myelosuppressive agents:** may increase the likelihood of myelosuppression

References

Brada M, Stenning S, Gabe R, *et al*. Temozolomide versus procarbazine, lomustine and vincristine in recurrent high-grade glioma. *J Clin Oncol* 2010;**28**(3):4601–8.

Hammond LA, Eckardt JR, Baker SD, *et al*. Phase I and pharmacokinetic study of temozolomide on a daily-for-5-days schedule in patients with advanced solid malignancies. *J Clin Oncol* 1999;**17**(8):2604–13.

Stupp R, Mason WP, van den Bent MJ, *et al*. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;**352**(10):987–96.

Teriflunomide

Teriflunomide is the second oral disease-modifying agent used in the treatment of MS. It was first marketed in the UK in 2013. It can be associated with hepatic impairment, and careful monitoring is therefore required.

Uses

Licensed uses

In the UK/USA

- *MS*: teriflunomide is licensed for relapsing forms of MS in the USA, and RRMS in the UK.

Presentation

- *Trade name*: Aubagio®. Generics are not available.
- *Formulations*: oral tablets: 7mg and 14mg.

Mechanism of action

Teriflunomide is a reversible inhibitor of dihydroorotate dehydrogenase, a mitochondrial protein used in pyrimidine synthesis. It prevents the proliferation of B and T lymphocytes. It may also alter cytokine production.

Toxicity and side effects

- *Common—cardiovascular*: hypertension. *Dermatological*: acne, alopecia, rash, and tinea infection. *Gastrointestinal*: diarrhoea, gastroenteritis, nausea, and vomiting. *Genitourinary*: increased urinary frequency and UTI. *Gynaecological*: menorrhagia. *Immunological*: hypersensitivity. *Musculoskeletal*: myalgia. *Neurological*: paraesthesiae and peripheral neuropathy. *Psychiatric*: anxiety. *Respiratory*: bronchitis and upper respiratory tract infections.
- *Serious—gastrointestinal*: hepatic impairment and pancreatitis. *Haematological*: neutropenia. *Musculoskeletal*: rhabdomyolysis. *Respiratory*: interstitial lung disease.

Contraindications

- *Absolute*: hypersensitivity, severe hepatic or renal impairment (Child–Pugh class C), severe active infection, pre-existing immunodeficiency, any significant cytopenia, and severe hypoproteinaemia.
- *Relative*: no dose adjustment is required in mild to moderate hepatic or renal impairment, but close monitoring is advised.

Use in special populations

- *Elderly*: separate studies have not been conducted in the elderly; however, the elderly experience an age-related deterioration in hepatic and renal function; hence caution is advised.
- *Pregnancy*: teriflunomide should not be used during pregnancy or in men wishing to father a child. Teriflunomide can take up to 2 years to be eliminated from the body, so pregnancy should be avoided for 2 years after discontinuation of the drug. This time can be reduced to a few weeks by taking activated charcoal or colestyramine.
- *Lactation*: breastfeeding is contraindicated.

Efficacy

In the TEMSO trial, the ARR was reduced to 0.37 in the teriflunomide 14mg treatment group, compared to 0.54 in the placebo group (relative reduction in ARR of 31.5%). Disability progression sustained for 3 months and 6 months was significantly reduced with teriflunomide treatment (20.2% of treated patients exhibited progression of disability sustained for 3 months, compared to 27.3% in the placebo group, and 13.8% of treated patients developed disability progression sustained at 6 months, compared to 18.7% with placebo). Teriflunomide treatment was associated with a 67% reduction in MRI total lesion volume and a 69% reduction in gadolinium-enhancing lesions, compared to placebo, after 2 years. The TOWER study showed similar results for the ARR and disability progression sustained at 3 months, but no significant difference in disability progression sustained at 6 months. The TENERE study comparing teriflunomide to high-dose SC IFN-β1a showed no significant differences in terms of treatment failure due to adverse events or lack of efficacy after 12 months and an equivalent effect on ARR reduction.

Dosing and monitoring

Dosing

Teriflunomide is administered PO as a daily dose of 14mg.

Routine monitoring LFTs should be checked prior to drug initiation, and monthly for the first 6 months. The drug should be stopped if liver injury is suspected. FBC and a renal profile should also be checked before initiation and during therapy, given the risk of cytopenias and kidney injury. All patients should be screened for latent TB infection prior to initiation. Patients should be monitored for symptoms or signs of infection, peripheral neuropathy, skin reactions, and hypertension. An accelerated elimination procedure using colestyramine (8g every 8h for 11 days) or activated charcoal (50g every 12h for 11 days) should be considered to reverse adverse reactions, given the slow elimination of teriflunomide from plasma. Teriflunomide can act as both a cytochrome P450 inhibitor and inducer. It may decrease the INR of patients on warfarin, and this should therefore be monitored. The administration of live vaccines should be avoided during treatment.

Pharmacokinetics and interactions

Pharmacokinetics

Maximal plasma concentrations are reached 1–4h following administration, with complete bioavailability, which is unaffected by food co-ingestion. The drug is extensively bound to plasma protein (>99%). The drug reaches steady-state concentration at ~3 months. It can be metabolized initially by hydrolysis or oxidation but is eliminated mainly through biliary excretion of unchanged drug. There is some renal excretion of metabolites. The median half-life is ~19 days.

Interactions See Table A.112.

Table A.112 Interactions of teriflunomide

Medications whose plasma levels are altered by teriflunomide	Pharmacodynamic interactions
Decreased levels: colestyramine and rifampicin	**Vaccinations:** administration of live vaccines should be avoided
Increased levels: cefaclor, oestrogens (including oral contraceptive pill), repaglinide, and rosuvastatin	**With warfarin:** can decrease the INR

References

O'Connor P, Wolinsky JS, Confavreux C, *et al*.; TEMSO Trial Group. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med* 2011;**365**(14):1293–303.

Confavreux C, O'Connor P, Comi G, *et al*.; TOWER Trial Group. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014;**13**(3):247–56.

Vermersch P, Czlonkowska A, Grimaldi LM *et al*.; TENERE Trial Group. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomized, controlled phase 3 trial. *Mult Scler* 2014;**20**(6):705–16.

Tetrabenazine

Tetrabenazine (TBZ) was first licensed in the UK in 2010 for the treatment of HD. It is the only medication licensed for this indication and acts by depleting central dopamine stores and thereby reducing the extent of choreiform movements. It does, however, carry with it the significant side effects of sedation and depression, and should only be used after careful discussion with the patient and their carers.

Uses

Licensed uses

In the UK/USA

- *Huntington's chorea*: TBZ is licensed for the treatment of chorea associated with HD in individuals aged 18 years and older.

Off-licence uses

- Chorea, hemiballismus, tardive dyskinesia (particularly dystonia), and tic disorders.

Presentation

- *Trade names*: Revcon®, Tetmodis®, and Xenazine®. Generics are not available.
- *Formulations*: TBZ is available as a tablet at doses of 12.5mg and 25mg.

Mechanism of action

In HD, there is an early overactivity of dopaminergic pathways. TBZ is a reversible inhibitor of type 2 vesicular monoamine transporters (VMAT2). These transporters are found on vesicles containing monoamine neurotransmitters, including dopamine, at nerve terminals. Inhibition prevents monoamine (primarily dopamine, but also serotonin and NA) uptake into these vesicles, preventing storage and release, resulting in overall depletion of monoamines by degradation within the cytoplasm. Part of the activity of TBZ may also be mediated by inhibition of post-synaptic dopamine receptors.

Toxicity and side effects

Most side effects are short-lived and can be alleviated by lowering the dose.

- *Common—gastrointestinal*: nausea, elevated liver enzymes, and weight gain (can be beneficial in HD patients where increased energy expenditure results in weight loss). *Neurological*: akathisia, insomnia, and sedation. *Endocrine*: hyperprolactinaemia.
- *Serious—cardiovascular*: QTc prolongation and syncope. *Neurological*: acute dystonic reactions, NMS, parkinsonism (rare and more likely to occur in older patients). *Psychiatric*: depression (more likely to occur in younger patients), suicidal ideation, and suicide. *Respiratory*: aspiration pneumonia.

Contraindications

- *Absolute*: hypersensitivity to TBZ or its excipients, concomitant use (or use within the previous 14 days) of MAOIs, and concomitant use (or use within the previous 20 days) of reserpine are contraindications. Depression or history of suicidality, history of prolactin-dependent tumours (e.g. breast and pituitary), parkinsonism, phaeochromocytoma, and breastfeeding are also contraindications.
- *Relative*: no dosage alteration is required in renal disease. In mild and moderate hepatic impairment, halve the initial dose, and uptitrate the dose slowly in the smallest increments. Patients with severe hepatic impairment have not been studied; therefore, additional caution is advised in these patients.

Uses in special populations

- *Elderly*: no dose adjustment is routinely required; however, the elderly are more prone to Parkinson-like side effects and hence should be monitored with caution.
- *Pregnancy*: there are little data with regard to the use of TBZ in pregnancy. The manufacturers recommend avoiding treatment, if possible.
- *Lactation*: breastfeeding is a contraindication during treatment.

Efficacy

A 12-week RCT (n = 84), undertaken by the Huntington Study Group, found a significant reduction of the Unified Huntington's Disease Rating Scale (UHDRS) score of 3.5 points with TBZ, compared to placebo (95% CI 5.2–1.9; p <0.0001). There was also a significant benefit on ratings of clinical global improvement (p = 0.0074). There were five serious adverse events reported, including suicide and restlessness/suicidal ideation. No overall improvement in functional scores was reported in this study, with some suggestion of functional decline in some measures. However, later analysis of these data, alongside unpublished data from CARE-HD, concluded that TBZ does not appear to have a negative effect on function and cognition, both of which are likely in accordance with normal disease progression.

The AAN guideline advises the use of up to 100mg/day where HD chorea requires treatment. However, they emphasize that trials have only been in HD patients with good baseline function, often mobile and with little cognitive decline or depression. They recommend that clinicians consider each case individually and decide on the appropriateness of treatment in view of possible mood disturbance, improvement in quality of life, polypharmacy, and cost.

Dosing and monitoring

Dosing

Start treatment at 12.5mg daily, and increase by 12.5mg every 3–4 days to 12.5mg bd, then tds. This can then be increased every 4 days, as required/tolerated. The usual maintenance dose is <100mg/day. The maximum recommended daily dose is 200mg/day.

Routine monitoring Monitor for depression and parkinsonism.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is low and highly variable, due to extensive hepatic first-pass metabolism by carbonyl reductase. Bioavailability is not effected by food. Hydroxytetrabenazine (α and β forms) are the major active metabolites. T_{max} for these metabolites is 1–1.5h, and they are 60–70% protein-bound. They are predominantly metabolized by CYP2D6 and have half-lives of 4–8h and 2–4h for the α and β forms, respectively. The drug is excreted as metabolites in the urine (75%) and faeces (7–16%).

A proportion of patients are poor metabolizers of hydroxytetrabenazine metabolite, due to low or absent CYP2D6 enzymes; a genetic test is available and recommended in the USA to assess the level of expression of CYP2D6 for patients requiring doses of TMZ higher than 50mg.

Interactions See Table A.113.

Table A.113 Interactions of tetrabenazine

Medications which alter tetrabenazine plasma levels	Pharmacodynamic interactions
Levels decreased: CYP2D6 inducers, e.g. rifampicin	**With CNS depressants:** can cause increased sedation
Levels increased: CYP2D6 inhibitors, e.g. SSRIs	**With drugs that prolong QTc:** may increase risk of arrhythmia
	With antipsychotics, amantadine, and metoclopramide: increased risk of extrapyramidal side effects

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Tiagabine

Tiagabine was first marketed in the UK as an AED in 1998. It is a narrow-spectrum AED, used as an adjunct in focal-onset epilepsy. It is limited by its potential to aggravate absence seizures. It benefits from having few pharmacokinetic interactions.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- *Epilepsy*: tiagabine is licensed, as an adjunct, for the treatment of focal-onset seizures in individuals aged 12 years and older.

Off-licence uses

- None.

Presentation

- *Trade names*: Gabitril®. Generics are not available.
- *Formulations*: tiagabine is available as a film-coated tablet in 5mg, 10mg, and 15mg doses.

Mechanism of action

The main mechanism of action of tiagabine is thought to be mediated by enhancing the effects of GABA. It acts selectively to inhibit GABA transporter-1, thereby inhibiting GABA uptake at neurons and glia.

Toxicity and side effects

Visual disturbances similar to vigabatrin are a theoretical concern, due to similarities in mechanisms of action (i.e. both elevate brain GABA concentrations), but have not been reported to date.

- *Common—gastrointestinal*: abdominal pain, diarrhoea, nausea, and vomiting. *Musculoskeletal*: muscle twitching. *Neurological*: ataxia, confusion, dizziness, speech disorder, and tremor. *Ophthalmological*: blurred vision. *Psychiatric*: aggression, depressed mood, difficulty concentrating, emotional lability, insomnia, and nervousness.
- *Serious—neurological*: encephalopathy and non-convulsive status epilepticus have been reported. *Psychiatric*: psychosis and suicidal ideation have been reported.

Contraindications

- *Absolute*: hypersensitivity to tiagabine or any of its excipients, and acute porphyria. Avoid in severe hepatic impairment.
- *Relative*: caution is advised in absence seizures where there is the risk of non-convulsive status epilepticus. Caution is also advised when used in individuals with a history of mood and psychotic disorders. In mild to moderate hepatic impairment, reduce the dose and/or prolong the dose interval. The dose does not need to be changed in individuals with renal impairment.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their hepatic function and may benefit from lower dosing regimens.
- *Pregnancy*: animal studies have not demonstrated teratogenic effects; however, there are no studies in humans. There are no data available as to changes in tiagabine pharmacokinetics during pregnancy, although tiagabine is highly protein-bound, and hence changes should be expected. Use in pregnancy depends on whether the benefits outweigh the potential risks.
- *Lactation*: it is not known whether tiagabine is present in human breast milk. If used, infants should be monitored for potential side effects and switched to an alternative feeding regimen if these are identified.

Efficacy

Several meta-analyses have looked at the clinical efficacy of tiagabine. A Cochrane review including six RCTs concluded that tiagabine use had an overall risk ratio for a 50% or greater reduction in seizures vs placebo of 3.16 (95% CI 1.97–5.07) for patients with drug-resistant focal-onset epilepsy. Further studies suggest it is less effective than topiramate and levetiracetam.

Dosing and monitoring

Dosing

Start treatment at 5–10mg daily in two divided doses. Increase by 5–10mg daily at weekly intervals. The normal maintenance dose depends on the presence of enzyme-inducing drugs. The normal maintenance dose is between 30mg and 45mg with enzyme-inducing drugs, and 15–30mg without them, given in 2–3 divided doses.

Routine monitoring Baseline FBC, liver and renal function tests are recommended. These should then be repeated yearly.

Therapeutic drug monitoring Optimum seizure control, when used in monotherapy, occurs at plasma concentrations of 20–200ng/L.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is ~90%; T_{max} is 0.5–2h. T_{max}, but not total bioavailability, is reduced by food co-ingestion. Steady state occurs at 1–2 days. Tiagabine is >95% protein-bound, predominantly to plasma albumin. It undergoes extensive hepatic metabolism by enzymes, including the cytochrome P450 system. The metabolites are inactive. Autoinduction does not occur. The half-life of tiagabine as a monotherapy is 5–9h. This is reduced to 2–4h in the presence of enzyme-inducing AEDs. ~2% of tiagabine is excreted unchanged by the renal system. The majority of the metabolites (>60%) are excreted in the faeces, the rest in the urine.

Interactions See Table A.114.

Table A.114 Interactions of tiagabine

Medications which alter tiagabine plasma levels	Medications whose plasma levels are altered by tiagabine
Levels decreased: carbamazepine, phenobarbital, phenytoin, pregabalin, and primidone	**Levels decreased:** valproate
Levels increased: cimetidine, naproxen, and salicylates	

References

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Tizanidine

Tizanidine is a hydantoin derivative with similar biochemistry to the α2-agonist clonidine. It first became available for the treatment of spasticity in the mid 1990s. It remains an effective first-line treatment for many patients with generalized spasticity of various aetiologies, although careful monitoring of BP and liver function is required.

Uses

Licensed uses

In the UK/USA

- *Spasticity*: tizanidine is licensed for the treatment of spasticity (in the UK, specifically spasticity secondary to MS, spinal cord injury, or disease) in individuals aged 18 years and older.

Presentation

- *Trade names*: Zanaflex®. Generics are available.
- *Formulations*: tizanidine is available as a capsule and a tablet. Capsules: 2mg, 4mg, and 6mg. Tablets: 2mg and 4mg.

Mechanism of drug action

Tizanidine is an α2-adrenergic agonist, which acts presynaptically, particularly at spinal interneurons, to cause a reduction in excitatory neurotransmitter release, and thus reducing the firing of spinal motor neurons.

Toxicity and side effects

- *Common—cardiovascular*: bradycardia, hypotension. *Dermatological*: pruritus, rash. *Gastrointestinal*: abdominal pain, constipation, diarrhoea, dyspepsia, LFT derangement, xerostomia. *Musculoskeletal*: back pain. *Neurological*: dizziness, dyskinesia, myasthenia. Paraesthesiae, somnolence, speech disorder, weakness. *Ophthalmological*: blurred vision. *Psychiatric*: anxiety, depression, delusions, hallucinations. *Respiratory*: fever, flu-like illness.
- *Serious—gastrointestinal*: fatal hepatotoxicity remains rare but has been reported.

Contraindications

- *Absolute*: hypersensitivity to tizanidine, significant hepatic impairment, and concurrent use of strong CYP1A2 inhibitors, i.e. ciprofloxacin and fluvoxamine.
- *Relative*: concurrent antihypertensive therapy. Other CYP1A2 inhibitors (fluoroquinolones, amiodarone, mexiletine, propafenone, verapamil, cimetidine, famotidine, oral contraceptives, aciclovir, and ticlopidine). Tizanidine should be used with caution and with slow uptitration of the dose in renal impairment (CrCl <25mL/min). Use is not recommended in hepatic impairment.

Uses in special populations

- *Elderly*: the elderly experience an age-related decline in hepatic and renal function; co-prescription of drugs, including antihypertensives, is also commoner; hence tizanidine should be used with caution.
- *Pregnancy*: use in pregnancy is not recommended, due to observed teratogenicity in animal studies.
- *Lactation*: tizanidine passes into breast milk in small quantities and should be avoided while breastfeeding.

Efficacy

There are a number of studies showing tizanidine to be superior to placebo for spasticity. A 2008 systematic review of 53 studies investigating the efficacy, pharmacokinetics, and tolerability of tizanidine (including several large multicentre RCTs from the UK and USA) concluded that tizanidine is at least as effective as baclofen in controlling spasticity secondary to MS or spinal cord injury and may be better tolerated. A 1998 meta-analysis of ten trials found tizanidine to be of comparable efficacy to baclofen and diazepam, with less muscle weakness and better overall tolerability.

Dosing and monitoring

Dosing

Start treatment at 2mg at night, increasing in 2mg/day increments every 3–4 days, up to a typical maintenance regime of 18–24mg/day in three or four divided doses. The maximum daily dose is 36mg.

Routine monitoring LFTs should be performed at baseline and monthly thereafter for the first 4 months. Discontinue tizanidine if there is evidence of hepatic dysfunction.

Discontinuation To minimize the risk of potentially serious rebound hypertension and tachycardia, tizanidine should be withdrawn slowly over a period of weeks, with regular monitoring of BP.

Pharmacokinetics and interactions

Pharmacokinetics

Tizanidine capsules and tablets have broadly similar pharmacokinetics when administered in the fasted state. There is extensive first-pass metabolism, resulting in 40% bioavailability. Time to peak plasma levels is 1h. When taken with food, tablets have higher, and capsules lower, plasma bioavailability. Time to peak plasma levels may also be delayed. Metabolism is predominantly via hepatic CYP1A2 enzymes to pharmacologically inactive metabolites, which are mainly excreted in the urine. Elimination half-life is ~2.5h.

Interactions See Table A.115.

Table A.115 Interactions of tizanidine

Medications which alter tizanidine plasma levels	Pharmacodynamic interactions
Levels increased: CYP1A2 inhibitors, in particular ciprofloxacin and fluvoxamine (combination contraindicated)	**With antihypertensives and MAOIs:** tizanidine may enhance hypotension **With beta-blockers:** tizanidine may intensify AV nodal blockade **With CNS depressants:** enhanced sedative effect of tizanidine **With mirtazapine, SNRIs, and TCAs:** may reduce the antispasticity effect of tizanidine

References

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Topiramate

Topiramate was first marketed in the UK as an AED in 1995. It is predominantly used in the management of headache and epilepsy. In epilepsy, it is a broad-spectrum AED, which can be used in most seizure types.

Uses

Licensed uses

In the UK/USA

- *Epilepsy*: topiramate is licensed as a monotherapy for focal-onset seizures and primary generalized tonic–clonic seizures (UK: in individuals aged 6 years and older; USA: individuals aged 10 years and older). As an adjunct, it is licensed in the treatment of focal-onset seizures with or without secondary generalization, primary generalized tonic–clonic seizures, and seizures associated with LGS in individuals aged 2 years and older (UK and USA).
- *Migraine*: topiramate is licensed for the prophylaxis of migraine in individuals aged 16 years and older in the UK, and aged 18 years and older in the USA.

Off-licence uses

- Absence seizures, ET, idiopathic intracranial hypertension, MOH, and prophylactic treatment of all TACs.

Presentation

- *Trade names*: Topamax®. Generics are available.
- *Formulations*: topiramate is available as a capsule, a film-coated tablet, and Sprinkle® capsules. Capsule: 15mg, 25mg, and 50mg. Film-coated tablet: 25mg, 50mg, 100mg, and 200mg. Sprinkle® capsules: 15mg, 25mg, and 50mg.

Mechanism of action

The exact mechanism of action of topiramate remains unclear. Several analgesic and antiepileptic actions have been proposed: (1) enhancement of GABA-mediated inhibition by a route distinct from benzodiazepines and barbiturates; (2) modulation of several different types of ion channel—it inhibits voltage-dependent sodium channels and L-type VGCCs, and it enhances the activity of potassium channels; and (3) weak carbonic anhydrase inhibitor activity.

Toxicity and side effects

Carbonic anhydrase inhibitors reduce intracellular pH, resulting in an increased incidence of hypokalaemia, metabolic acidosis, nephrolithiasis, paraesthesiae, polydipsia, and polyuria.

- *Common—dermatological*: alopecia, pruritus, and rash. *Gastrointestinal*: anorexia, changes in weight (loss is commoner than gain), diarrhoea, and nausea are the commonest side effects. Abdominal pain, constipation, dry mouth, dyspepsia, gastritis, oral paraesthesiae, and vomiting. *Haematological*: anaemia. *Musculoskeletal*: arthralgia, muscular weakness, and myalgia. *Neurological*: confusion, dizziness,

fatigue, and paraesthesiae are the commonest side effects. Cognitive impairment, dysarthria, dysgeusia, impaired coordination and memory, seizures, tremor, and vertigo can also occur. *Ophthalmological*: blurred and double vision. *Psychiatric*: aggression, anxiety, depression, and mood swings. *Respiratory*: dyspnoea, epistaxis, and rhinorrhoea.

- *Serious—dermatological*: Stevens–Johnson syndrome and toxic epidermal necrolysis have been reported. *Gastrointestinal*: pancreatitis can occur. *Haematological*: leucopenia and neutropenia. *Immunological*: hypersensitivity reactions have been reported. *Ophthalmological*: there have been rare reports of topiramate triggering secondary angle-closure glaucoma. This usually happens within a month of treatment and may be associated with choroidal effusions, and lens or iris displacement. Specialist ophthalmological advice and withdrawal of topiramate as soon as possible is recommended. *Psychiatric*: mania, psychosis, and suicide have been reported.

Contraindications

- *Absolute*: hypersensitivity to topiramate or its excipients.
- *Relative*: topiramate should be avoided in individuals at risk of metabolic acidosis, acute porphyria, and urinary calculi. Topiramate is renally excreted; hence if the GFR is <60mL/min/1.73m^2, use with caution at a lower dose. If the eGFR is <30mL/min/1.73m^2, then use half of the normal dose. Caution and lower dosing regimens are advised in individuals with moderate to severe hepatic impairment, as topiramate undergoes extensive hepatic metabolism.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function, and may benefit from lower dosing regimens.
- *Pregnancy*: animal studies have demonstrated teratogenic effects, but there are few studies in humans. During pregnancy, topiramate plasma levels can decrease by up to 40%, so a higher dose may be required. Use in pregnancy involves weighing up the potential benefits and side effects (see Antiepileptic drugs in young women, pp. 37–9).
- *Lactation*: breastfed infants of mothers medicated with topiramate experience plasma levels 9–17% of maternal levels. If used, infants should be monitored for potential side effects and switched to an alternative feeding regimen if these are identified.

Efficacy

- *Epilepsy*: the SANAD study, a large unblinded RCT conducted in the UK, suggested that, for the treatment of focal-onset epilepsy, 12-month remission with topiramate, lamotrigine, and carbamazepine was similar. However, lamotrigine performed significantly better than topiramate in terms of time to treatment failure.
- *ET*: topiramate was the first oral medication to be studied in a large multicentre, double-blind, placebo-controlled trial of ET (n = 208). Patients with moderate to severe ET were given 24 weeks of treatment with placebo or topiramate (average final dose 292mg/day). There was a significant improvement in tremor rating scales of 29%, compared

to 16% with placebo (p <0.001), as well as in improvement in function and disability (p = 0.001). However, 40% of patients experienced side effects, leading to a high dropout rate from the trial.

- *Headache*: topiramate is recommended as a first-line migraine prophylactic agent in adults. A Cochrane review of six trials demonstrated that topiramate at 100mg and 200mg was consistently more effective than placebo in reducing headache frequency. In one trial, there was a 53% response rate in the topiramate group, significantly higher than 23% in the placebo group. Topiramate use in cluster headache and SUNCT has also been evaluated in open-label studies and has been shown to be effective in inducing remission in patients who have not responded to first-line prophylactic agents. Topiramate has also been shown in RCTs to reduce the frequency of headache days in MOH. In one study, it significantly reduced the number of headache days per month by 6.4, compared with 4.7 days for placebo.

Dosing and monitoring

Dosing

Start treatment at 25mg once at night for 1 week. This can then be increased by 25–50mg/day in 1- to 2-weekly intervals and should be given in two divided doses.

- *Epilepsy*: when used as monotherapy, the normal maintenance dose is 100–200mg in two divided doses. The recommended maximum is 250mg bd, although doses of 500mg bd have been used.

  When used as an adjunct, the normal maintenance dose is 200–400mg daily in two divided doses. The maximum recommended dose is 400mg/day.
- *ET*: doses can be titrated up, as required/tolerated, to a maximum dose of 400mg/day.
- *Headache*: in migraine, 50–100mg in divided doses is typical; the maximum dose is 200mg daily. In cluster headache, 200mg daily in divided doses is the typical dose. In SUNCT, studies have used doses of 50–300mg, and, in MOH, doses of up to 200mg are used.

Routine monitoring FBC and LFTs are recommended at baseline, 2 months, and every 6 months thereafter, while treatment is continued. Patients should be monitored for cognitive side effects and mood disturbances.

Therapeutic drug monitoring Plasma concentrations for optimum seizure control, when used in monotherapy, in adults are 5–20mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

The oral bioavailability of topiramate is >80%. T_{max} is 2–3h. Neither of these parameters are affected by food co-ingestion. Steady state is reached in 4–5 days. 15% of topiramate is protein-bound. Only ~20% of topiramate is hepatically metabolized, although this is increased in the presence of enzyme-inducing drugs to ~50%. Six metabolites are formed, none of which are pharmacologically active. Autoinduction does not occur. Over 80% of the topiramate dose is excreted via the renal system. Up to 60%

of topiramate is excreted unchanged in the urine. The half-life in adults not on enzyme-inducing therapy is 20–30h, and with enzyme-inducing therapy 10–15h.

Interactions See Table A.116.

Table A.116 Interactions of topiramate

Medications which alter topiramate plasma levels	Medications whose plasma levels are altered by topiramate	Pharmacodynamic interactions
Levels decreased: carbamazepine, eslicarbazepine acetate, oxcarbazepine, phenobarbital, phenytoin, primidone, and valproate **Levels increased:** amitriptyline, lithium, metformin, propranolol, and sumatriptan	**Levels decreased:** digoxin, eslicarbazepine acetate, glibenclamide, pioglitazone, risperidone, sumatriptan, and valproate **Levels increased:** amitriptyline, haloperidol, hydrochlorothiazide, lithium, metformin, and phenytoin	**With other carbonic anhydrase inhibitors and bicarbonate:** there is an increased risk of renal calculi formation **With levetiracetam:** increased risk of weight loss **With valproate:** increased risk of encephalopathy

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Trientine dihydrochloride

Trientine dihydrochloride is a copper-chelating agent used in the management of WD. It was first marketed in the UK in 1985. Its main advantage over penicillamine is its better side effect profile, although exacerbation of neurological symptoms may be slightly more likely with trientine, compared to penicillamine.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- *Inborn errors of metabolism*: trientine is licensed for the treatment of WD in individuals of all ages who are intolerant of D-penicillamine.

Off-licence uses

- None.

Presentation

- *Trade names*: Syprine®. Generics are available in the UK.
- *Formulations*: trientine is available as a capsule at doses of 250mg (USA) and 300mg (UK).

Mechanism of action

WD is characterized by the accumulation of copper in the liver, brain, and other tissues. This occurs secondary to impaired function of ATP7B, an enzyme required to bind copper to caeruloplasmin, allowing the release of copper into the bloodstream. Trientine is a copper-chelating agent, which binds copper atoms and is subsequently excreted by the urinary tract, thereby reducing total systemic levels of copper.

Toxicity and side effects

- *Common—dermatological*: rash. *Gastrointestinal*: nausea.
- *Serious—gastrointestinal*: severe colitis and duodenitis have been reported. *Haematological*: anaemia (rarely). *Neurological*: dystonia and MG have been reported in marketed use. *Respiratory*: asthma and bronchitis.

Contraindications

- *Absolute*: hypersensitivity to trientine dihydrochloride.
- *Relative*: studies have not been performed in patients with hepatic or renal impairment; hence no guidance with regard to dose adjustment can be recommended.

Uses in special populations

- *Elderly*: there are no data on the safety and efficacy of trientine in patients above 65 years of age; use with caution.
- *Pregnancy*: trientine has been shown to be teratogenic in animal studies, but there are insufficient data regarding its safe use in pregnant women with WD. Its use in pregnancy should be done only after careful consideration of the benefits and risks of treatment.
- *Lactation*: it is not known whether trientine is excreted in breast milk, and caution should be taken when given to nursing mothers.

Efficacy

Trientine is effective at treating neurological symptoms of WD but also carries a significant risk of provoking further neurological deterioration. A multicentre, retrospective analysis of data on 380 patients with WD who were treated with D-penicillamine or trientine monotherapy showed similar clinical efficacies; ~55% of patients with either agent used as monotherapy showed neurologic improvement in their symptoms. With regard to side effects, treatment with trientine had a lower rate of side effects requiring discontinuation, when compared with penicillamine, but neurologic deterioration occurred more frequently in patients who were given trientine first: ~2% (n = 6/295) with penicillamine vs ~10% (n = 4/38) with trientine (p = 0.018).

A randomized, double-blinded, two-arm study compared the efficacy of trientine and tetrathiomolybdate in treating 48 patients with the neurological presentation of WD. While trientine was better tolerated (4.3% of patients developed adverse effects, compared to 28% receiving tetrathiomolybdate), it had a significantly higher rate of neurological deterioration, compared to tetrathiomolybdate (26% vs 4%; p <0.05).

Dosing and monitoring

Dosing

Start treatment at 750–1250mg/day daily in 2–4 divided doses, given before food. This can be then adjusted up to a maximum of 2.4g/day, depending on the biochemical and clinical response.

Routine monitoring Monitoring with 24h urinary copper analysis every 6–12 months should be undertaken. FBC should be regularly undertaken to look for the development of iron deficiency anaemia.

Pharmacokinetics and interactions

Pharmacokinetics

Data on the pharmacokinetics of trientine are not available.

Interactions See Table A.117.

Table A.117 Interactions of trientine dihydrochloride

Medications which alter trientine plasma levels	Medications whose plasma levels are altered by trientine
Levels decreased: zinc	**Levels decreased:** zinc and serum iron

References

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Unfractionated heparin

Unfractionated heparin is a parenteral anticoagulant that is used in a variety of clinical settings. It was first discovered in 1916 and was marketed in the UK for the first time in 1939.

Uses

Licensed uses

In the UK/USA

Unfractionated heparin is licensed for the treatment of deep vein thrombosis and pulmonary embolism in individuals of all ages in the UK, and the treatment of all forms of venous thrombosis in the USA.

Off-licence uses

- None.

Presentation

- *Trade names*: widely available in generic form.
- *Formulations*: heparin is available as a concentrate for infusion or injection. Heparin sodium is available at the following doses: 1000iu/mL in 1mL, 5000iu in 5mL, 10 000iu in 10mL, and 20 000iu in 20mL ampoules.

Mechanism of action

Heparin is an anticoagulant that acts by inhibiting thrombin and potentiating the naturally occurring inhibitors of activated factor X (Xa).

Toxicity and side effects

- *Common—dermatological*: alopecia, purpura, rash. *Endocrine*: hyperkalaemia, osteoporosis. *Gastrointestinal*: diarrhoea, nausea, vomiting. *Haematological*: anaemia, thrombocytopenia. *Immunological*: injection site reactions, fever. *Urological*: haematuria.
- *Serious—dermatological*: skin necrosis. *Gastrointestinal*: gastrointestinal haemorrhage, rectal haemorrhage, haematemesis, pancreatitis, melaena. *Haematological*: heparin-induced thrombocytopenia, priapism. *Neurological*: intracranial haemorrhage. *Respiratory*: haemothorax.

Contraindications

- *Absolute*: hypersensitivity to heparin or its excipients, patients who consume large amounts of alcohol, active bleeding, haemophilia or other bleeding disorders, severe liver disease (including oesophageal varices), purpura, severe hypertension, active TB, or increased capillary permeability. Patients with present or previous thrombocytopenia. The rare occurrence of skin necrosis in patients receiving heparin contraindicates the further use of heparin either by SC or IV routes because of the risk of thrombocytopenia. Because of the risk of post-operative haemorrhage, heparin is contraindicated during surgery of the brain, spinal cord, and eye, in procedures at sites where there is a risk of bleeding, in patients who have had recent surgery, and in patients undergoing LP or regional anaesthetic block.
- *Relative*: those who are deemed to be at high risk of bleeding. In patients with advanced renal disease and mild to moderate renal impairment, a reduction in dosage may be necessary to reduce the risk of bleeding.

Uses in special populations

- *Elderly*: no dosing adjustment is required in the elderly, although there is an increased risk of bleeding; hence heparin should be used with caution.
- *Pregnancy*: heparin is not contraindicated in pregnancy. Heparin does not cross the placenta. Haemorrhage may be a problem during pregnancy or after delivery.
- *Lactation*: as a result of its high molecular weight, it is not excreted in breast milk and hence can be used by nursing mothers.

Efficacy

- Cerebral sinus thrombosis (see Low-molecular-weight heparin, e.g. tinzaparin, pp. 506–7).

Dosing and monitoring

Dosing

As the effects of heparin are short-lived, administration by IV infusion is preferable to intermittent IV injections. This should be given as a loading dose of 5000 units IV and a maintenance dose of 1000–2000 units/h by IV infusion (or by 5000–10 000 units 4-hourly IV injection).

Routine monitoring Daily laboratory monitoring (ideally at the same time each day, starting 4–6h after initiation of treatment) is essential during full-dose heparin treatment, with adjustment of the dosage to maintain an aPTT value 1.5–2.5 times midpoint of the normal range or control value. Platelet counts should be measured in patients receiving heparin treatment for longer than 5 days, and the treatment should be stopped immediately in those who develop thrombocytopenia.

Pharmacokinetics and interactions

Pharmacokinetics

After injection, heparin extensively binds to plasma proteins. Heparin is metabolized in the liver, and the inactive metabolic products are excreted in the urine. The half-life of heparin is dependent on the dose.

Interactions See Table A.118.

Table A.118 Interactions of unfractionated heparin

Pharmacodynamic interactions
With antiplatelets, anticoagulants, dipyridamole, iloprost, NSAIDs: increased risk of bleeding
With nitrates: reduced anticoagulant effect of heparins
With ACE inhibitors, angiotensin receptor II antagonists, and aliskiren: increased risk of hyperkalaemia

References

Coutinho J, de Bruijn SF, Deveber G, Stam J. Anticoagulation for cerebral venous sinus thrombosis. *Cochrane Database Syst Rev* 2011;**8**:CD002005.

Einhaupl K, Villringer A, Meister W, *et al*. Heparin treatment in sinus venous thrombosis. *Lancet* 1991;**338**(8767):597–600.

Valproate

Valproate was first marketed in the UK as an AED in 1974. It is a broad-spectrum AED, often used first-line in primary generalized seizures where no other AED has been shown to be more effective (although others may have fewer side effects). It is thought to be less effective, when compared to carbamazepine, in focal-onset seizures. Its main disadvantages are its adverse effect profile, marked teratogenic potential, non-linear pharmacokinetics, and substantial drug interactions.

Uses

Licensed uses

In the UK

- *Epilepsy*: valproate is licensed as a monotherapy or as an adjunct for the treatment of any form of epilepsy in patients of any age.

In the USA

- *Epilepsy*: valproate is licensed as monotherapy and adjunctive therapy for the treatment of complex partial seizures occurring either in isolation or in association with other types of seizures and in the treatment of simple and complex absence seizures. It is also licensed for use as an adjunct, but not as a monotherapy, for the treatment of patients with multiple seizure types, including absence seizures.
- *Migraine*: valproate is licensed for the prophylaxis of migraine in individuals aged 12 years and older.

Off-licence uses

- Refractory status epilepticus and Sydenham's chorea.

Presentation

- *Trade names*: Convulex®, Depacon®, Depakene®, Depakote®, Epilim®, Epilim Chrono®, Epilim Chronosphere®, Epilim IV®, Episenta®, Epival®, and Stavzor®. Generics are available.
- *Formulations*: valproate is available as sodium valproate, valproate semisodium, and valproic acid. Valproic acid has a one-to-one dose relationship with sodium valproate. Valproate semisodium (Depakote®) is a compound of sodium valproate and valproic acid in a 1:1 molar relationship. Valproate semisodium is the only valproate derivative licensed in the treatment of mania.
  1. Sodium valproate is available PO in both standard and modified-release formulations and as a powder and solution for IV injection. Standard-release formulations include a crushable tablet, an enteric-coated tablet, a liquid, an oral solution, and a syrup. Crushable tablet: 100mg. Enteric-coated tablet: 200mg and 500mg. Liquid: 200mg/5mL. Oral solution: 200mg/5mL. Syrup: 200mg/5mL. Modified-release formulations include a capsule, granules, and a tablet. Capsule: 150mg and 300mg. Granules: 50mg, 100mg, 250mg, 500mg, and 750mg. Tablet: 200mg, 300mg, and 500mg. Powder for injection: 400mg/vial. Solution for injection: 100mg/mL in a 3mL ampoule.

2. Valproate semisodium is available as an enteric-coated tablet at doses of 250mg and 500mg.
3. Valproic acid is available as enteric-coated tablets in doses of 150mg, 300mg, and 500mg.

Mechanism of action

The dominant mechanism of action in epilepsy or migraine has not been conclusively established. Sodium valproate raises levels of GABA, possibly through inhibition of its metabolism, e.g. by inhibiting GABA transaminase. It has also been shown to reduce high-frequency neuronal activity, possibly by blockade of voltage-sensitive sodium channels or by activation of calcium-dependent potassium channels. This may reduce epileptic activity and the cortical spreading depression which underlies migraine pathogenesis. In addition, valproate has been shown (*in vitro*) to reduce meningeal inflammatory extravasation, a process which is thought to occur in migraine.

Toxicity and side effects

- *Common—dermatological*: patients commonly experience alopecia; this is usually temporary, however, and the hair may grow back curly. *Endocrine*: dysmenorrhoea and hyponatraemia. *Gastrointestinal*: diarrhoea, gastritis, and nausea are common initially. Weight gain is common with long-term use. The main concern is hepatic dysfunction which can be severe, particularly in at-risk groups: young children <3 years old, patients with congenital defects in enzymes involved in the urea cycle, and individuals with seizure disorders associated with prominent learning impairment. Raised LFTs are common and usually transient. Unless severe or associated with a raised prothrombin time, continued monitoring of liver function, rather than discontinuing valproate treatment, is appropriate. *Haematological*: thrombocytopenia (usually dose-related) is common; monitor platelet counts over 100 000 without intervention. Anaemia is also common (macrocytic). *Neurological*: confusion, convulsion, deafness, extrapyramidal disorders (especially tremor), fatigue, headache, memory impairment, and nystagmus. *Psychiatric*: aggression and impaired attention.
- *Serious—cardiovascular*: vasculitis. *Dermatological*: rarely, angio-oedema, Stevens–Johnson syndrome, and toxic epidermal necrolysis have been reported. *Gastrointestinal*: severe liver damage, including failure, and pancreatitis have been rarely reported. *Haematological*: leucopenia and pancytopenia. Rarely, bone marrow failure, myelodysplasia, and red cell aplasia can occur. *Immunological*: rarely SLE. *Neurological*: encephalopathy and coma can occur secondary to hyperammonaemia.

Of note, less commonly, syndrome of inappropriate antidiuretic hormone (SIADH), hypothyroidism, PCOS, a reversible Fanconi syndrome, and osteoporosis can develop with use of valproate.

Contraindications

- *Absolute*: active liver disease, personal or family history of severe hepatic impairment, hypersensitivity to valproate or its excipients, and acute porphyria.
- *Relative*: hepatic impairment, history of pancreatitis, suspected mitochondrial disorder, thrombocytopenia, and suspected urea cycle disorders. The dose should be reduced at increasingly severe levels of renal impairment.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their hepatic and renal function. They are also more likely to have pharmacokinetic interactions with other co-prescribed medications and are more commonly predisposed to side effects, including sedation and reduced nutritional intake, and hence lower dosing regimens are often appropriate.
- *Pregnancy*: sodium valproate has a marked teratogenic effect, including the risk of fetal neural tube defects. Use in pregnancy involves weighing up the potential benefits and side effects (see Antiepileptic drugs in young women, pp. 37–9). If the medication is continued, then high-strength folic acid should be given throughout pregnancy. Prophylactic vitamin K should be given to minimize bleeding risks. Valproate levels decrease markedly during pregnancy; hence, if treatment is to be continued, rises in the dose may be required.
- *Lactation*: breastfed infants are exposed to serum valproate levels 4–12% of maternal levels. If valproate treatment is continued during breastfeeding, then infants should be monitored for adverse effects, including haematological effects, and, if these are identified, the infant should be switched to an alternative feeding regimen.

Efficacy

- *Epilepsy*: a large multicentre, unblinded RCT in 2007 (the SANAD study) looked at the comparative efficacy and tolerability of lamotrigine, valproate, and topiramate in generalized epilepsy. It found clear evidence that valproate was more effective than lamotrigine and more tolerable than topiramate, and hence should be considered first-line in the treatment of generalized epilepsy. In contrast, a multicentre, double-blind trial carried out in 1992 comparing the efficacy of valproate with carbamazepine in focal-onset epilepsy demonstrated that carbamazepine gave better long-term control of seizures and had fewer side effects than valproate. For discussion of the use in status epilepticus, see Status epilepticus, pp. 41–5.
- *Migraine*: a Cochrane review of valproate in migraine prophylaxis found that patients were twice more likely to experience a ≥50% reduction in headache frequency with sodium valproate, compared to placebo.

Dosing and monitoring

Dosing

- For the treatment of all forms of epilepsy:
  - *oral administration*: start treatment at 600mg daily in 1–2 divided doses. Increase by up to 300mg in 3-day intervals up to a normal maintenance dose of 1–2g daily in two divided doses. The recommended maximum is 2.5g daily in two divided doses;
  - *IV administration*, age >12 years: start treatment with a 10mg/kg IV injection; then treatment can be continued in three ways: (1) continuous IV infusion; (2) IV injection in 2–4 divided doses; and (3) intermittent IV infusion in 2–4 divided doses. The normal total maintenance dose is 20–30mg/kg/day up to a maximum of 2.5g daily. If switching between PO and IV methods of administration, then give the current dose of oral medication IV.
- *Migraine*: start treatment at 200mg bd, and increase, as required, to 1200–1500mg daily in divided doses.

Routine monitoring Liver function and FBC should be assessed at baseline and 2 months, and 6-monthly thereafter. Platelet function tests should be considered preoperatively. Vitamin D monitoring and DEXA scans should be considered in individuals considered at risk of osteoporosis. Weight should be monitored throughout treatment.

Therapeutic drug monitoring Optimum seizure control, when used in monotherapy, occurs at plasma concentrations of 50–100mg/L. In migraine, levels of valproate should be measured every 2–3 months. A target should be aimed of between 21 and 50 micrograms/mL, as this has been shown in one study to reduce the frequency of headache further than higher serum levels (50–100 micrograms/mL).

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is >90% for standard-release medications. Oral bioavailability is higher with enteric-coated and suspension formulations, compared to extended-release tablets. The doses of extended-release preparations need to be 10–20% greater than normal preparations to have equivalent bioavailability. Food co-ingestion prolongs T_{max} but does not affect bioavailability. T_{max} is 1.5h with standard preparations and syrup, 3–7h with enteric-coated and granular formulations, and longer with extended-release formulations. Valproate is 90% bound to plasma proteins (less in the elderly due to reduced albumin levels).

Valproate undergoes extensive hepatic metabolism to multiple metabolites via the cytochrome P450 enzyme system. Valproic acid glucuronide and 3-oxo-valproic acid constitute just over one-third of these metabolites each. Some of the minor metabolites are pharmacologically active at a similar level to valproate. Autoinduction does not occur. More than 97% of valproate is renally excreted, the majority as metabolites and ~3% as unchanged drug. In adults without co-prescription of enzyme inducers, the half-life is 12–16h. With enzyme inducers, the half-life is 5–9h in adults.

Interactions See Table A.119.

Table A.119 Interactions of valproate

Medications which alter valproate plasma levels	Medications whose plasma levels are altered by valproate	Pharmacodynamic interactions
Levels decreased: aciclovir, amikacin, carbamazepine, carbapenems*, cisplatin, diflunasil, eslicarbazepine acetate, ethosuximide, lamotrigine, methotrexate, naproxen, oral contraceptives, panipenem, phenobarbital, phenytoin, primidone, rifampicin, ritonavir, and topiramate **Levels increased:** acetylsalicylic acid, chlorpromazine, clobazam, felbamate, fluoxetine, isoniazid, sertraline, and stiripentol	**Levels decreased:** phenytoin and topiramate **Levels increased:** amitriptyline, aripiprazole, carbamazepine–epoxide metabolite of carbamazepine, clomipramine, chlorpromazine, diazepam, ethosuximide, felbamate, lamotrigine, lopinavir, lorazepam, midazolam, naproxen, nimodipine, nortriptyline, paroxetine, phenobarbital, rufinamide, and zidovudine	**With clonazepam:** may cause absence status **With lithium:** increased risk of lithium neurotoxicity **With cisplatin:** increased risk of thrombocytopenia and neutropenia

* As a result of the magnitude of the interaction between carbapenem antibiotics (e.g. ertapenem, imipenem, meropenem, and panipenem) and valproate whereby valproate plasma levels are decreased to almost non-detectable values, these drug combinations can be considered contraindicated.

References

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Linde M, Mulleners WM, Chronicle EP, McCrory DC. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. *Cochrane Database Syst Rev* 2013;**6**:CD010611.

Marson AG, Al-Kharusi AM, Alwaidh M, *et al*. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007;**369**(9566):1016–26.

Mattson RH, Cramer JA, Collins JF. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group. *N Engl J Med* 1992;**327**(11):765–71.

Verapamil

Verapamil, a calcium channel blocker, is the first-line prophylactic agent for episodic and chronic cluster headache. Its efficacy for these indications was first established in the 1980s. It is given in far higher doses than for cardiovascular indications, and so patients are at particular risk of bradycardia and heart block.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- It is licensed for the management of a range of cardiological disorders, including angina, arrhythmias, and hypertension. It is not licensed for the treatment of neurological disorders.

Off-licence uses

- Prophylaxis of cluster headache.

Presentation

- *Trade names*: Calan®, Cordilox®, Verelan®, Zolvera®. Generics are available.
- *Formulations*: verapamil is available as an oral solution and a standard tablet. Oral solution: 40mg/5mL. Standard tablet: 40mg, 80mg, 120mg, and 160mg.

Mechanism of action

Verapamil is a calcium channel blocker and has been shown to block P-type calcium channels in the rat striatum. It may also block N- and Q-type calcium channels. Verapamil may exert its predominant effect by inhibiting calcium channels in the hypothalamus, i.e. the site where cluster headaches are believed to originate. Verapamil also has inhibitory activity on potassium channels, particularly the HERG (human ether-a-go-go related gene) potassium channel, and part of its efficacy may rely on HERG potassium channel blockade in the CNS.

Toxicity and side effects

- *Common—cardiovascular*: angina on abrupt withdrawal of treatment, ankle swelling, bradycardia, hypotension. *Gastrointestinal*: constipation, nausea, and vomiting.
- *Serious—cardiovascular*: asystole, heart block, heart failure. *Dermatological*: Stevens–Johnson syndrome.

Contraindications

- *Absolute*: acute porphyria, bradycardia, hypotension (systolic BP <90mmHg), known hypersensitivity, second- and third-degree AV block (unless pacemaker *in situ*), severe left ventricular systolic dysfunction, sick sinus syndrome (unless pacemaker *in situ*), AF/atrial flutter with accessory pathway (e.g. Wolff–Parkinson–White syndrome).

- *Relative*: hypertrophic cardiomyopathy. In severe hepatic impairment, verapamil should be reduced to one-third of the normal dose, and titration should be done carefully, with close monitoring of the heart rate and rhythm. Careful monitoring should also be undertaken in renal impairment, as there are limited data on verapamil toxicity in renal disease.

Uses in special populations

- *Elderly*: with increasing age, there is reduced clearance of verapamil, and so accumulation is more likely. This increases the risk of cardiovascular adverse effects, such as AV block and sinus bradycardia, so elderly patients on verapamil should be closely monitored with regular ECGs and careful dose titration.
- *Pregnancy*: verapamil crosses the placental barrier, and studies in rats have shown that verapamil can cause fetal death and delayed growth when given in levels toxic to the mother. There are no reported cases of teratogenicity associated with verapamil use in humans. Use with caution in pregnancy, and avoid in the first trimester.
- *Lactation*: verapamil has been detected in breast milk, but the amount is thought to be too small to be harmful to the infant.

Efficacy

In a double-blind, randomized, placebo-controlled trial of 30 patients with cluster headache, 12 of the 15 patients on verapamil experienced a >50% reduction in headache frequency after taking verapamil for 2 weeks. Half of these experienced a reduction in headache frequency within the first week of treatment, while, at the end of 2 weeks, four patients in the verapamil group were headache-free. None in the placebo group experienced a reduction in headache frequency. The dose of verapamil used was 120mg tds, and side effects were minimal, with no test subject discontinuing treatment due to side effects.

Dosing and monitoring

Dosing

Start treatment at 120–160mg tds, with titration of 80mg every 2 weeks. The dose needed for effective prophylaxis varies considerably between patients; the range is 240–960mg. Some patients may require doses as high as 1200mg.

Routine monitoring Regular ECG monitoring is advised when increasing the dose of verapamil and also once established on a stable dose, due to the risk of AV block and bradycardia.

Pharmacokinetics and interactions

Pharmacokinetics

Verapamil is well-absorbed from the gut but undergoes extensive first-pass metabolism, so only 10–30% of the oral dose is bioavailable. It is a racemic mixture composed of (R)-verapamil and (S)-verapamil. It reaches peak concentrations at 1–2h. Verapamil is metabolized by the hepatic cytochrome P450 system, mainly by the enzyme CYP3A4, to less active metabolites,

which are largely excreted by the kidneys. It is 90% plasma protein-bound. In single doses, the mean half-life is 2–8h, and, with repeated dosing, this increases to 4.5–12h. Metabolism is reduced in liver dysfunction, and the half-life can increase to 14–16h.

Interactions See Table A.120.

Table A.120 Interactions of verapamil

Medications which alter plasma levels of verapamil	Medications whose plasma levels are altered by verapamil	Pharmacodynamic interactions
Levels increased: atorvastatin, macrolide antibiotics, sirolimus **Levels decreased:** cimetidine, rifampicin, phenobarbital, St John's wort	**Levels increased:** alcohol, carbamazepine, colchicine, ciclosporin, dabigatran, digoxin, ivabradine, lenalidomide, midazolam, simvastatin, sirolimus, theophylline	**With antiarrhythmics:** increased risk of myocardial depression and AV block **With antihypertensives, e.g. α-blockers:** risk of profound hypotension **With β-blockers:** increased risk of asystole **With lithium:** increased risk of neurotoxicity **With inhalational anaesthetic agents:** increased risk of myocardial depression

References

Gabai I, Spierings E. Prophylactic treatment of cluster headache with verapamil. *Headache* 1989;**29**(3):167–8.

Leone M, D'Amico D, Frediani F, *et al*. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. *Neurology* 2000;**54**(6):1382–5.

Vigabatrin

Vigabatrin was first marketed in the UK as an AED in 1989. It is a narrow-spectrum drug, predominantly used in the treatment of infantile spasms. Its main limitation to be used as a broader-spectrum agent in epilepsy is its high incidence of visual field defects. These are considered acceptable in infantile spasms because of the potential benefits, but are not acceptable in focal-onset epilepsy where safer alternative AEDs are readily available.

Uses

Licensed uses

In the UK

- *Epilepsy*: vigabatrin is licensed as a monotherapy for the treatment of infantile spasms. It is also licensed for use as an adjunct in the treatment of refractory focal-onset epilepsy with or without secondary generalization, which has not been controlled with all other suitable AEDs. Both indications are for individuals of all ages.

In the USA

- *Epilepsy*: vigabatrin is licensed as an adjunct for the treatment of refractory complex partial seizures in adults who have not adequately responded to alternative treatments and in whom the potential benefits outweigh the risk of visual loss. In addition, it is licensed as a monotherapy for the treatment of infantile spasms in children aged 1 month to 2 years old.

Off-licence uses

- None.

Presentation

- *Trade names*: Sabril®. Generics are not available.
- *Formulations*: vigabatrin is available as a film-coated tablet and a powder for oral solution. Film-coated tablet: 500mg. Powder: 500mg/sachet.

Mechanism of action

The mechanism of action of vigabatrin is irreversible inhibition of GABA transaminase, the enzyme responsible for the breakdown of GABA. This potentiates the inhibitory action of GABA within the CNS, reducing the spread of epileptic discharges.

Toxicity and side effects

- *Common—gastrointestinal*: abdominal pain, nausea, and weight gain. *Neurological*: dizziness, fatigue, headache, impaired attention and memory, paraesthesiae, speech disorder, and tremor. *Ophthalmological*: visual field defects have been reported in up to a third of patients. The defects are typically a concentric constriction in both eyes, more prominent nasally than temporally. These defects occur months to years following initiation of treatment and may be dose- and length of treatment-dependent. The majority of patients with these defects are asymptomatic and hence have to be monitored, using

perimetry-based visual field techniques, regularly. The cause of these visual field defects is not clear. It may be as a result of an idiosyncratic drug reaction or an accumulation of vigabatrin in the retina. Subsequent optic neuritis and atrophy have been reported, and it is recommended that vigabatrin is discontinued when field defects are detected.
Psychiatric: aggression, agitation, depression, excitation, nervousness, and paranoia.

- *Serious—dermatological*: angio-oedema is rare. *Gastrointestinal*: rarely hepatitis. *Neurological*: encephalopathy and movement disorders. *Psychiatric*: reports of mania, psychosis, and suicide.

Contraindications

- *Absolute*: hypersensitivity to vigabatrin or its excipients, and pre-existing visual field defects.
- *Relative*: vigabatrin should not be used in certain types of epilepsy—it can aggravate absence seizures and induce an absence-type status epilepticus. It may also exaggerate myoclonic seizures. Caution should be taken if other retinotoxic drugs are prescribed and if there is a prior history of behavioural problems, depression, or psychosis. Reduced doses are required in moderate to severe renal impairment. No dose adjustment is required in hepatic impairment.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal function and may benefit from lower dosing regimens.
- *Pregnancy*: animal studies have demonstrated teratogenic effects; however, there are no studies in humans. No information is available on pharmacokinetic changes of vigabatrin during pregnancy. Use in pregnancy involves weighing up the potential benefits and side effects.
- *Lactation*: 4–20% of maternal plasma levels are present in breast milk. No studies have been performed to assess the level of vigabatrin in breastfed infants. If used, infants should be monitored for potential side effects, and, if these are identified, the infant should be switched to an alternative feeding regimen.

Efficacy

As an adjunct in focal-onset epilepsy, with or without secondary generalization, the proportion of patients experiencing a 50% or more reduction in seizure frequency was 48% vs 26% for placebo in one double-blind, placebo-controlled trial.

Dosing and monitoring

Dosing

- For the adjunctive treatment of focal-onset seizures, age >18 years: start treatment at 500–1000mg/day in 1–2 divided doses for 1 week. Increase by 500mg each week. The normal maintenance dose is 2–3g daily in 1–2 divided doses. The maximum recommended dose is 3g.

Routine monitoring Baseline FBC, and renal and liver function tests should be performed, and these should be monitored at least yearly. Visual field testing should be conducted at baseline and then 6-monthly. Weight should also be monitored during treatment.

Therapeutic drug monitoring Measurement of plasma levels may be useful in ascertaining compliance where doses of between 1 and 3g/day would be expected to have plasma levels of 0.8–36mg/L. It should be noted that vigabatrin continues to work long after the medication has been stopped, due to irreversible blockage of GABA transaminase.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is 60–80%. T_{max} is 1–2h. Neither bioavailability nor T_{max} are affected by food co-ingestion. Steady state is reached in 1–2 days. Vigabatrin has 0% protein binding and undergoes no hepatic metabolism. ~100% is excreted unchanged by the renal system. The half-life in a healthy adult is 5–8h; this is directly proportional to the eGFR.

Interactions See Table A.121.

Table A.121 Interactions of vigabatrin

Medications which alter vigabatrin plasma levels	Medications whose plasma levels are altered by vigabatrin
Levels decreased: felbamate	**Levels decreased:** phenytoin and rufinamide

References

Bruni J, Guberman A, Vachon L, *et al*. Vigabatrin as add-on therapy for adult complex partial seizures: a double-blind, placebo-controlled multicentre study. The Canadian Vigabatrin Study Group. *Seizure* 2000;**9**(3):224–32.

Maguire MJ, Hemming K, Wild JM, *et al*. Prevalence of visual field loss following exposure to vigabatrin therapy: a systematic review. *Epilepsia* 2010;**51**(12):2423–31.

Vincristine

Vincristine is one of a group of drugs known as the vinca alkaloids. It was first licensed for use in the 1960s, initially in the treatment of leukaemia, although its indications have subsequently expanded. Within the context of brain tumours, it is used with procarbazine and lomustine as PCV triple therapy. It has synergistic antineoplastic effects with these agents. Its main limitations are its peripheral neurotoxic effects. Its myelosuppressive effects are relatively mild, compared to other chemotherapeutic agents.

Uses

Licensed uses

In the UK

- *Haematological*: vincristine is licensed for use in malignant lymphomas, multiple myeloma, idiopathic thrombocytopenic purpura, and leukaemia in individuals of all ages.
- *Solid tumours*: vincristine is licensed for use in both paediatric and adult solid tumours.

In the USA

- *Haematological*: vincristine is licensed for use in the treatment of leukaemia and lymphoma.
- *Solid tumours*: vincristine is licensed for use in the treatment of neuroblastoma, rhabdomyosarcoma, and Wilms' tumour.

Off-licence uses

- The treatment of CNS tumours, usually in conjunction with procarbazine and lomustine, as part of PCV chemotherapy.

Presentation

- *Trade names*: Oncovin® and Vincasar PFS®. Generics are available.
- *Formulations*: vincristine is available as a solution for IV injection at concentrations of 1mg/mL in 2mL and 5mL vials.

Mechanism of action

Vincristine inhibits neoplastic cell proliferation by binding to tubulin, thus preventing microtubule formation and stopping cell cycling during metaphase. It may also block glutamic acid utilization, thereby impairing protein synthesis.

It is highly lipophilic but is thought to poorly penetrate the blood–brain barrier due to the presence of drug efflux pumps, e.g. P-glycoproteins, in healthy cerebral capillaries. The mechanism by which it enters the brain parenchyma and affects brain tumours is thus unclear but may be due to peritumoural disruption of the blood–brain barrier.

Toxicity and side effects

- *Common—dermatological*: alopecia and rash. Injection site reactions—vincristine is a vesicant. *Gastrointestinal*: gastrointestinal disturbance, including abdominal pain, constipation, diarrhoea, and weight loss, can occur. *Haematological*: leucopenia (although, compared to other

vinca alkaloids, vincristine causes negligible myelosuppression). *Ophthalmological*: transient cortical blindness.
- *Serious—gastrointestinal*: impaction and intestinal obstruction. *Immunological*: anaphylaxis has been reported. *Neurological*: peripheral neuropathy can be dose-limiting—often starting with sensory impairment and paraesthesiae, progressing to neuropathic pain and motor difficulties. These may reduce with a reduction in dose but can persist. *Ophthalmological*: optic atrophy, leading to blindness, can occur. *Renal*: uric acid nephropathy. *Respiratory*: acute shortness of breath and severe bronchospasm.

It is often fatal if mistakenly given by the intrathecal route.

Contraindications

- *Absolute*: hypersensitivity to vincristine or its excipients, and patients with demyelinating variants of Charcot–Marie–Tooth disease.
- *Relative*: previous spinal irradiation or peripheral neurological disease may have an additive neurotoxic effect with vincristine. Vincristine undergoes hepatic metabolism; hence a 50% reduction in the dose is advised if bilirubin level is >51 micromol/L. No dose adjustment is required in renal disease.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in hepatic function, and hence liver function will need to be cautiously monitored. Elderly patients may also be more susceptible to both the urological and neurological adverse effects.
- *Pregnancy*: vincristine is teratogenic in humans. Women of childbearing age should be offered contraception and advised to avoid becoming pregnant.
- *Lactation*: vincristine levels within breast milk is unknown. Mothers should be given advice about the benefits of breastfeeding vs the potential adverse effects of the drug and offered alternative methods of feeding.

Efficacy

Within the context of brain tumours, vincristine is usually administered as part of the PCV chemotherapy regimen (see Lomustine, pp. 503–5 for further discussion of the evidence).

Vincristine appears to be effective in this regimen, even though it has well-documented low penetration across the blood–brain barrier. A meta-analysis of trials investigating the treatment of high-grade glioma, looking specifically at whether addition of vincristine to the chemotherapeutic regimen makes a difference to survival, demonstrated a statistically significant synergistic benefit of adding vincristine to procarbazine and lomustine.

Dosing and monitoring

Dosing

The dosage of vincristine varies, depending on the BSA, clinical indication, local protocols, individual toxicity, and other adjuvants used in the

chemotherapy regimen. Readers are advised to follow local guidelines. Typical regimens use doses of 1.4–1.5mg/m^2, with a maximum dose of 2mg/week.

Routine monitoring Prior to initiation of treatment, FBC, and renal and liver function should be assessed. An FBC should be repeated regularly during therapy.

Pharmacokinetics and interactions

Pharmacokinetics

Vincristine has very poor oral bioavailability and hence needs to be administered by IV infusion. Its pharmacokinetics have a triphasic serum decay pattern, with half-lives at 5min, 2.3h, and 85h. Terminal half-life can be between 19h and 155h in humans. Over 90% distributes from serum to tissue within 30min. Metabolism is mediated primarily hepatically by the CYP3A system. 80% of the injected drug is ultimately excreted in the faeces, and the rest in the urine.

Interactions See Table A.122.

Table A.122 Interactions of vincristine

Medications which alter vincristine plasma levels	Medications whose plasma levels are altered by vincristine	Pharmacodynamic interactions
Levels decreased: agents that increase the CYP3A subfamily of cytochrome P450 activity, e.g. bosentan, anticonvulsants, reverse transcriptase inhibitors **Levels increased:** agents that inhibit the CYP3A, e.g. itraconazole, protease inhibitors, macrolide antibiotics	**Levels decreased:** phenytoin	**With allopurinol, pyridoxine, and isoniazid:** may increase the incidence of myelosuppression

References

Van den Bent MJ, Brandes AA, Taphorn MJ, *et al*. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol* 2013;**31**(3):344–50.

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Warfarin

Warfarin is an oral coumarin anticoagulant that is widely used in the prevention of thrombosis and treatment of thromboembolic disease. It was first marketed in the UK in the 1950s and remains the most frequently used oral anticoagulant.

Uses

Licensed uses

In the UK/USA

- *Prevention of stroke*: warfarin is licensed for prophylaxis of systemic embolization in patients considered to be at risk of cardio-embolic stroke from AF, metallic heart valves, and ischaemic or rheumatic heart disease in individuals of all ages.
- *Treatment of venous thrombosis*: warfarin is also licensed for the treatment of venous thrombosis in individuals of all ages.

Off-licence uses

- Cryptogenic stroke.

Presentation

- *Trade names*: Coumadin®, Marevan®, and Jantoven®. Generics are available.
- *Formulations*: warfarin is available as a hard tablet and a powder for reconstitution and IV injection (USA). Hard tablet: 0.5mg, 1mg, 2mg (USA), 2.5mg (USA), 3mg, 4mg (USA), 5mg, 6mg (USA), 7.5mg (USA), and 10mg (USA). Powder for injection: 5mg vial.

Mechanism of action

Warfarin is a synthetic coumarin anticoagulant. It acts by inhibiting the formation of active clotting factors II, VII, IX, and X, as well as the anticoagulant proteins C, S, and Z. The precursors of these factors require the carboxylation of their glutamic acid residues by γ-carboxy glutamic acid to allow the coagulation factors to bind to phospholipid surfaces on the vascular endothelium. This reaction requires reduced vitamin K and is catalysed by γ-glutamyl carboxylase; the carboxylation is coupled to the oxidation of vitamin K to its epoxide. Vitamin K epoxide is reduced to vitamin K by vitamin K epoxide reductase complex-1 (VKORC-1). Warfarin directly inhibits VKORC-1, resulting in the synthesis of partially decarboxylated coagulation factors, with markedly impaired coagulant activity.

Toxicity and side effects

- *Common—dermatological*: purpura, rash. *Gastrointestinal*: diarrhoea, jaundice, nausea, and vomiting.
- *Serious—dermatological*: skin necrosis. *Gastrointestinal*: gastrointestinal haemorrhage, pancreatitis. *Haematological*: anaemia, epistaxis, thrombocytopenia. *Immunological*: allergic reaction. *Neurological*: intracranial haemorrhage. *Respiratory*: haemothorax. *Urological*: haematuria.

Contraindications

- *Absolute*: known hypersensitivity to warfarin or any of its excipients. Haemorrhagic stroke, clinically significant bleeding, within 72h of major surgery with risk of severe bleeding, within 48h post-partum, pregnancy, and drugs where interactions may lead to a significantly increased risk of bleeding.
- *Relative*: ischaemic stroke—in patients with AF, long-term treatment with warfarin is beneficial, but the risk of early recurrent embolism is low, and therefore a break in treatment after ischaemic stroke is justified to reduce the risk of haemorrhagic conversion. Warfarin treatment should be restarted 2–14 days following ischaemic stroke, depending on the size of the infarct and BP. In patients with large embolic strokes or uncontrolled hypertension, warfarin treatment should be stopped for 14 days. The INR should be measured more frequently in patients with hepatic or renal disease.

Uses in special populations

- *Elderly*: the elderly are more at risk of bleeding, due to a combination of higher levels of hepatic impairment, renal impairment, falls, hypertension, and concomitant use of drugs which may alter INR levels. This group should have their INR monitored more frequently.
- *Pregnancy*: warfarin is teratogenic in the first trimester. There is also an increased risk of placental, fetal, and neonatal haemorrhage, particularly when used in the final weeks of gestation and at delivery. Hence warfarin shoud be avoided in pregnancy, particularly in the first and third trimesters.
- *Lactation*: warfarin is not present in milk in significant amounts and hence is considered safe for use by nursing mothers.

Efficacy

In the context of prevention of cardio-embolic stroke secondary to AF, numerous trials (SPAF-I, SPAF-II, SPAF-III, AFASAK, BAATAF, SPINAF, and CAFA) have demonstrated a two-third relative risk reduction of stroke in patients treated with dose-adjusted warfarin, compared to placebo, and a 39% relative risk reduction of stroke in patients treated with warfarin, compared to antiplatelet agents. The risk of major bleeding in patients on warfarin varies from 1.3% to 7.2% per year, depending on the population studied.

Dosing and monitoring

Dosing

Induction dose varies, depending on the age and indication. Follow local protocols. A typical induction dose is 5–10mg daily for 2 days, with subsequent doses calculated depending on INR levels.

Monitoring INR levels should be tested at regular intervals. Once the maintenance dose is established, it is rarely necessary to alter it. Those at high risk of bleeding benefit from more frequent INR monitoring. The target INR for most patients is 2–3 for the prevention of stroke in AF and for the treatment of venous thrombosis.

Pharmacokinetics and interactions

Pharmacokinetics

Warfarin is completely absorbed from the gastrointestinal tract. T_{max} is reached in ~4h. ~99% of the drug is bound to plasma proteins. Its effective plasma half-life is higly variable and ranges from 20h to 60h; the terminal half-life is ~7 days. It is metabolized in the liver, and 92% is excreted in the urine, mainly as metabolites. In the liver, it is metabolized by various CYP isoenzymes, including CYP 2C9, 2C19, 2C8, 2C18, 1A2, and 3A4.

Interactions See Table A.123.

Table A.123 Interactions of warfarin

Medications which alter warfarin plasma levels	Pharmacodynamic interactions
Levels decreased: CYP2C9 inhibitors, e.g. carbamazepine, phenytoin. CYP1A2 inhibitors, e.g. omeprazole, phenytoin. CYP3A4 inhibitors, e.g. carbamazepine and phenytoin	**With anticoagulants, antiplatelets, NSAIDs:** increased risk of haemorrhage
Levels increased: CYP2C9 inhibitors, e.g. amiodarone and fluconazole; CYP1A2 inhbitors, e.g. aciclovir, oral contraceptives, and verapamil; CYP3A4 inhibitors, e.g. amlodipine, cimetidine, and ranitidine	**With alcohol:** variation in alcohol intake can affect anticoagulant control **With sulfonylureas:** coumarins possibly enhance hypoglycaemia

References

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Zinc acetate

Zinc acetate is used in the treatment of WD. Its relatively safe side effect profile and low cost have meant it is often considered the preferred long-term maintenance therapy for WD. It was first marketed in the UK in 2004.

Uses

Licensed uses

In the UK/USA

- *Inborn errors of metabolism*: zinc acetate is licensed for the treatment of WD in individuals of all ages. In the USA, it is only licensed as maintenance therapy after initial treatment with a chelating agent.

Off-licence uses

- None.

Presentation

- *Trade names*: Galzin® and Wilzin®. Generics are not available.
- *Formulations*: zinc acetate is available as 25mg and 50mg capsules.

Mechanism of action

WD is characterized by the accumulation of copper in the liver, brain, and other tissues. This occurs secondary to impaired function of ATP7B, an enzyme required to bind copper to caeruloplasmin, allowing the release of copper into the bloodstream. Zinc salts induce enterocyte and hepatocyte metallothionein, a protein which binds to copper atoms with high affinity. Copper binding in enterocytes prevents absorption of copper from food and reabsorption of copper from bile and other gastrointestinal secretions. Copper is then trapped in the enterocytes and eventually lost during desquamation. The induction of hepatic metallothionein may have an additional beneficial effect by sequestering body copper in a non-toxic hepatic pool.

Toxicity and side effects

- *Common—gastrointestinal*: abdominal discomfort (10% of patients); this side effect may be reduced if the dose is taken with some protein or if the first dose is delayed to mid morning. It is common for serum amylase, lipase, and ALP to be mildly elevated in the first few weeks of treatment.
- *Serious—haematological*: leucopenia, sideroblastic anaemia (both uncommon); likely to occur because of bone marrow suppression which may have resulted from copper deficiency.

Contraindications

- *Absolute*: hypersensitivity to zinc acetate.
- *Relative*: caution should be taken when treating patients with portal hypertension, as there is a risk of hepatic decompensation when switching from a copper-chelating agent. No dose adjustment is necessary in patients with renal impairment.

Uses in special populations

- *Elderly*: there are no data on the safety and efficacy of zinc acetate in patients above 65 years of age; use with caution.
- *Pregnancy*: limited data from animal studies show no harmful effects of zinc acetate treatment in pregnancy. There are no controlled studies in humans. The dose of zinc acetate should be reduced to 25mg tds and further adjusted, according to serum copper concentration and urinary copper excretion. Over-treatment may cause copper deficiency and may be especially harmful to the neonate, as copper is required for normal growth and mental development.
- *Lactation*: zinc is present in breast milk and should be avoided, if possible, as it may cause zinc-induced copper deficiency in the infant.

Efficacy

There are no multicentre prospective RCTs to estimate the efficacy of zinc monotherapy in WD. Generally, zinc acetate is given as maintenance therapy in symptomatic patients already treated with a chelating agent or in asymptomatic patients. A systematic review of one randomized trial and 12 observational studies of low validity suggested that zinc acetate monotherapy had a clinical efficacy similar to that of penicillamine in treating patients with WD who were asymptomatic or had neurological symptoms—90% of patients on zinc acetate treatment had favourable clinical outcomes (remained asymptomatic or improved). In a single-centre randomized trial (included in the systematic review), 81% of patients receiving zinc acetate as the initial therapy showed favourable clinical outcomes. In another prospective study, 13 pre-symptomatic patients with WD were successfully treated with zinc acetate, and, over the follow-up period (3–9 years), none of them developed symptoms related to WD. Furthermore, zinc acetate monotherapy seems to be a better initial treatment choice than penicillamine in asymptomatic patients with WD or those with neurological symptoms—zinc acetate treatment has a milder side effect profile, and there is a lower risk of initial neurological deterioration, when compared to penicillamine therapy.

Dosing and monitoring

Dosing

Zinc acetate has a slow onset of action; hence, in symptomatic patients, it is usually used either after copper detoxification with a chelating agent or as an adjunct with a chelating agent. It can be used as monotherapy in asymptomatic patients. Start treatment at 50mg tds. This dose can be adjusted, according to biochemical and clinical response, up to a maximum of 50mg five times daily.

Routine monitoring Routine monitoring for anaemia, leucopenia, and decreased high-density lipoprotein (HDL) cholesterol levels should be undertaken (early manifestations of copper deficiency). Monitoring with 24h urinary copper analysis every 6–12 months should be undertaken to ensure biochemical effectiveness. Measurements of urinary and/or plasma zinc may be useful in monitoring treatment compliance.

Pharmacokinetics and interactions

Pharmacokinetics

Pharmacokinetic evaluations based on zinc levels in blood are not useful, as its major site of action is the enterocyte. It is eliminated primarily through the faeces.

Interactions See Table A.124.

Table A.124 Interactions of zinc acetate

Medications which alter zinc plasma levels	Medications whose plasma levels are altered by zinc
Levels decreased: oral iron, penicillamine, and trientine	**Levels decreased:** ciprofloxacin, levofloxacin, movifloxacin, penicillamine, tetracyclines, and trientine

References

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Zonisamide

Zonisamide was first marketed in the UK as an AED in 2005. It is a broad-spectrum drug. It is the drug of choice for progressive myoclonic epilepsy and a second-line agent for focal-onset epilepsy. It benefits from having few pharmacokinetic interactions but is limited by its side effect profile.

Uses

Licensed uses

In the UK

- *Epilepsy*: zonisamide is licensed as an adjunct or a monotherapy for the treatment of focal-onset seizures with or without secondary generalization in individuals aged 18 years and older.

In the USA

- *Epilepsy*: zonisamide is licensed for the treatment as an adjunct of focal-onset seizures in individuals aged 18 years and older.

Off-licence uses

- Absence seizures, ET, and myoclonic epilepsy.

Presentation

- *Trade names*: Zonegran®. Generics are available.
- *Formulations*: zonisamide is available as a capsule at doses of 25mg, 50mg, and 100mg.

Mechanism of action

The mechanism of drug action has not been fully established. *In vitro* studies have shown it modulates GABA-mediated inhibition of neurons. In addition, it blocks voltage-sensitive calcium and sodium channels, thereby suppressing neuronal firing. It also acts as a carbonic anhydrase inhibitor.

Toxicity and side effects

Carbonic anhydrase inhibitors reduce intracellular pH, resulting in an increased incidence of hypokalaemia, metabolic acidosis, nephrolithiasis, paraesthesiae, polydipsia, and polyuria.

- *Common—dermatological*: alopecia, pruritus, and rash. *Gastrointestinal*: abdominal pain, constipation, diarrhoea, dyspepsia, nausea, and weight loss. *Neurological*: ataxia, bradyphrenia, confusion, dizziness, fatigue, impaired attention and memory, nystagmus, speech disorder, and tremor. *Ophthalmological*: double vision. *Psychiatric*: agitation, anxiety, depression, insomnia, irritability, and labile affect. *Urological*: nephrolithiasis and UTI.
- *Serious—dermatological*: rarely, Stevens–Johnson syndrome and toxic epidermal necrolysis have been reported. *Gastrointestinal*: cholecystitis, hepatocellular damage, and pancreatitis. *Haematological*: agranulocytosis, aplastic anaemia, and pancytopenia have been reported. *Immunological*: drug-induced hypersensitivity syndrome has been reported. *Musculoskeletal*: rhabdomyolysis has been reported. *Neurological*: coma, convulsions, myasthenic syndrome, NMS, and status epilepticus have been reported. *Psychiatric*: psychosis and suicide have been reported. *Urological*: rarely hydronephrosis and renal failure.

Contraindications

- *Absolute*: hypersensitivity to the sulfonamides, zonisamide, or any of its excipients, and severe hepatic impairment.
- *Relative*: caution is recommended in those predisposed to urinary calculi or with co-prescribed medications that can contribute to metabolic acidosis. In mild to moderate hepatic impairment, doses should be increased more slowly, every 2 weeks, rather than weekly, and lower maintenance doses may be required. In renal impairment, doses should be increased more slowly, every 2 weeks, rather than weekly, and the medication discontinued if there is a clinically significant deterioration in the eGFR. Doses may need to be lowered in progressively worsening renal impairment.

Uses in special populations

- *Elderly*: as a result of an age-related reduction in hepatic and renal function, the elderly are more commonly predisposed to side effects, particularly urinary calculi and dehydration, and lower doses are advised.
- *Pregnancy*: animal studies have demonstrated teratogenic effects; however, there are no studies in humans. There is no information available as to possible changes in pharmacokinetics during pregnancy. Use in pregnancy involves weighing up the potential benefits and side effects.
- *Lactation*: zonisamide is present in breast milk. Breastfed infants will have plasma levels equivalent to that of their mother. The manufacturer's advice is to avoid breastfeeding for the duration of treatment and for 4 weeks after treatment has ceased.

Efficacy

Several RCTs of zonisamide used as an adjunct in focal-onset epilepsy in patients already receiving 1–3 AEDs demonstrated a >50% reduction in seizure frequency in 28–47% of patients vs 12–22% with placebo. A large randomized, double-blind, parallel-group trial demonstrated that zonisamide monotherapy was non-inferior to carbamazepine in the treatment of newly diagnosed focal-onset epilepsy.

Dosing and monitoring

Dosing

- *For the treatment of epilepsy as an adjunct*: start treatment at 25mg bd. This is increased after 1 week to 50mg bd and then can be increased by 50mg bd per week. The normal maintenance dose is 300–500mg in two divided doses.
- *For the treatment of epilepsy as monotherapy*: start treatment at 100mg od for a fortnight. Then increase to 200mg/day for a fortnight, and then increase to 300mg/day. The normal maintenance dose is 300mg/day, although this can be increased by 100mg in fortnightly intervals to 500mg.

Routine monitoring Consider serum bicarbonate monitoring for metabolic acidosis, and regular renal function testing.

Therapeutic drug monitoring Optimum seizure control, when used in monotherapy, occurs at plasma concentrations of 10–40mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is >90%. T_{max} is 2–5h. T_{max} may be prolonged, but total bioavailability is not affected, by food co-ingestion. 40–50% is protein-bound. Steady state is reached in 10–15 days. 65% of zonisamide is metabolized, primarily via CYP3A4 to 2-sulfamoylacetyl phenol which is subsequently glucuronidated. There is no autoinduction. The metabolites are inactive. Zonisamide, the unchanged drug (35%), and its metabolites are almost entirely eliminated by the renal system. The half-life varies, depending on the presence of enzyme-inducing AEDs. The half-life is ~50–70h without co-prescribed enzyme inducers, and 25–35h with co-prescribed enzyme inducers.

Interactions See Table A.125.

Table A.125 Interactions of zonisamide

Medications which alter zonisamide plasma levels	Medications whose plasma levels are altered by zonisamide	Pharmacodynamic interactions
Levels decreased: carbamazepine, phenobarbital, phenytoin, primidone, and risperidone	Levels increased: carbamazepine–epoxide metabolite of carbamazepine	With other carbonic anhydrase inhibitors and bicarbonate: increased risk of renal calculi formation With CNS depressants, e.g. alcohol and MAOIs: increased risk of sedation

References

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