The Maudsley®

Prescribing Guidelines in Psychiatry

15TH EDITION

David M. Taylor
Thomas R. E. Barnes
Allan H. Young

WILEY Blackwell

The Maudsley® Prescribing Guidelines in Psychiatry

The Maudsley Guidelines

Other books in the *Maudsley Prescribing Guidelines* series include:

The Maudsley Practice Guidelines for Physical Health Conditions in Psychiatry
David Taylor, Fiona Gaughran, Toby Pillinger

The Maudsley Guidelines on Advanced Prescribing in Psychosis
Paul Morrison, David Taylor, Phillip McGuire

The Maudsley Prescribing Guidelines for Mental Health Conditions in Physical Illness
Siobhan Gee, David M. Taylor

The Maudsley Deprescribing Guidelines: Antidepressants, Benzodiazepines, Gabapentinoids and Z-drugs
Mark Horowitz, David M. Taylor

The Maudsley® Prescribing Guidelines in Psychiatry

15th Edition

David M. Taylor, **BSc, MSc, PhD, FFRPS, FRPharmS, FRCP$_{Edin}$, FRCPsych$_{Hon}$**

Director of Pharmacy and Pathology, Maudsley Hospital and
Professor of Psychopharmacology, King's College, London, UK

Thomas R. E. Barnes, **MBBS, MD, FRCPsych, DSc**

Emeritus Professor of Clinical Psychiatry at Imperial College London and joint head of the Prescribing Observatory for Mental Health at the Royal College of Psychiatrists' Centre for Quality Improvement, London, UK

Allan H. Young, **MB, ChB, MPhil, PhD, FRCP, FRCPsych**

Chair of Mood Disorders and Director of the Centre for Affective Disorders in the Department of Psychological Medicine in the Institute of Psychiatry, Psychology and Neuroscience at King's College, London, UK

WILEY Blackwell

This edition first published 2025

Registered Office(s)
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, New Era House, 8 Oldlands Way, Bognor Regis, West Sussex, PO22 8NQ, UK

For details of our global editorial offices, customer services, and more information about Wiley products visit us at www.wiley.com.

The manufacturer's authorized representative according to the EU General Product Safety Regulation is Wiley-VCH GmbH, Boschstr. 12, 69469 Weinheim, Germany, e-mail: Product_Safety@wiley.com.

Wiley also publishes its books in a variety of electronic formats and by print-on-demand. Some content that appears in standard print versions of this book may not be available in other formats.

Library of Congress Cataloging-in-Publication Data Applied for:

Paperback: 9781394238767

Cover Design: Wiley

Set in 10/12pt Sabon by Straive, Pondicherry, India

Contents

Preface

The *Maudsley® Prescribing Guidelines in Psychiatry* is now just one of several books in the Maudsley® *Guidelines* series. Since the publication of the 14th edition of the 'big' *MPG*, it has been joined by the *Maudsley® Deprescribing Guidelines: Antidepressants, Benzodiazepines, Gabapentinoids and Z-drugs* and by the *Maudsley® Prescribing Guidelines for Mental Health Conditions in Physical Illness*. These books cover some of the ground usually tackled in the main *MPG* but in much greater detail. In an effort to reduce repetition we have, in this 15th edition, left out (or let out) sections on such subjects as delirium, psychotropics in surgery and alternative routes of antidepressant administration and considerably reduced the size of sections on stopping psychotropics. What space has been made available by these changes has been filled by new sections on, for example, premenstrual syndrome, menopause, gambling disorder, ADHD in adults and relational aspects of prescribing practice.

This 15th edition of the *MPG* appears at a time when there is a growing antipathy towards the use of psychotropic drugs in mental illness. The prescribing advice given here assumes a decision to prescribe has already been made and so, to a large extent, we skirt the issue of whether or not prescribing is necessarily the right thing to do. Nonetheless, we do acknowledge that drug treatment is not always the best treatment for everyone in every situation. There are of course a range of effective non-drug treatments for mental health problems. The advice and guidance given in this and previous editions is aimed at optimising prescribing practice rather than promoting prescribing *per se*.

As ever, I and my fellow authors are indebted to a large number of expert contributors who have enabled us to provide information and guidance on such a wide range of topics; a feature that is possibly unique to the *Maudsley® Prescribing Guidelines in Psychiatry*. Sincere thanks are also due to Ivana Clark, the managing editor of this edition.

Even though some sections have been transplanted to other books in *The Guidelines* series, the scope of this edition is greater than the last and, as a consequence, it is a weightier book. It is probably worth pointing out that a special effort has been made to be economic with words and references although I suspect this is of little consolation to those lugging the book from ward to ward or home to hospital. It is the 'big' *MPG*, after all.

David M. Taylor
January 2025

Acknowledgements

The following have contributed to the 15th edition of *The Maudsley® Prescribing Guidelines in Psychiatry*.

Aditya Sharma
Alys Cawson
Andrea Danese
Anna Walder
Bruce Clark
Daniel Harwood
Daniel Hayes
David Rogalski
Delia Bishara
Derek Tracy
Dimitrios Chartonas
Ebenezer Oloyede
Emily Finch
Emmert Roberts
Eromona Whiskey
Ewa Zadeh
Faiza Hoda
Frankie Anderson
Haroula Konstantinidou
Ian Osborne
Ilaria Bonoldi
Ivana Clark
Jacob Kranowski
Justin Sauer
Kalliopi Vallianatou
Kate Organ
Livia Martucci
Mariam Mustapha
Marinos Kyriakopoulos
Mark Horowitz
Marta Di Forti
Martina Carboni
Mary Thornton
Michael Craig
Michael Newson
Michele Sie
Mike Kelleher
Nicola Funnell
Nicola Kalk
Nicoletta Adamo
Oliver Howes
Paul Gringras
Paul Moran
Petrina Douglas-Hall
Phillip Timms
Ray McGrath
Shubhra Mace
Siobhan Gee
Stephanie Lewis
Tennyson Lee
Thomas Reilly
Yuya Mizuno

Contributors' conflict of interest

Many of the contributors to *The Guidelines* have received funding from pharmaceutical manufacturers for research, consultancy or lectures. Readers should be aware that these relationships inevitably colour opinions on such matters as drug selection or preference.

We cannot therefore guarantee that guidance provided here is free of indirect influence of the pharmaceutical industry but hope to have mitigated this risk by providing copious literature support for statements made. As regards direct influence, no pharmaceutical company has been allowed to view or comment on any drafts or proofs of *The Guidelines* and none has made any request for the inclusion or omission of any topic, advice or guidance. To this extent, *The Guidelines* have been written independent of the pharmaceutical industry.

List of abbreviations

5HT3	5-hydroxytryptamine 3
22q11.2DS	22q11.2 deletion syndrome
%w/v	percentage weight per volume
AACAP	American Academy of Child and Adolescent Psychiatry
ACE	angiotensin-converting enzyme
Ach	acetylcholine
AChE	acetylcholinesterase
AChE-I	acetylcholinesterase inhibitors
ACOG	American College of Obstetricians and Gynecologists
AD	Alzheimer's disease
ADAPT	Adolescent Depression Antidepressants and Psychotherapy Trial
ADAS-cog	Alzheimer's Disease Assessment Scale – cognitive subscale
ADH	alcohol dehydrogenase
ADHD	attention deficit hyperactivity disorder
ADIS	Anxiety Disorders Interview Schedule
ADL	activities of daily living
ADR	adverse drug reactions
AEC	Anticholinergic Effect on Cognition Scale
AF	atrial fibrillation
AIDS	acquired immune deficiency syndrome
ALAI	aripiprazole long-acting injection
ALP	alkaline phosphate
ALT	alanine aminotransferase
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AN	anorexia nervosa
ANC	absolute neutrophil count
ANI	asymptomatic neurocognitive impairment
APP	amyloid precursor protein
ARIA	amyloid-related imaging abnormality
ART	antiretroviral therapy
ASD	autism spectrum disorder
AST	aspartate aminotransferase
ATPase	adenosine triphosphatase
AUD	alcohol use disorder
AUDIT	Alcohol Use Disorders Identification Test
Aβ	beta amyloid
BAC	blood alcohol concentration
BAP	British Association for Psychopharmacology
BBB	blood–brain barrier
bd	twice a day
BDD	body dysmorphic disorder

BDNF	brain-derived neurotrophic factor
BED	binge eating disorder
BEN	benign ethnic neutropenia
BMI	body mass index
BN	bulimia nervosa
BNF	*British National Formulary*
BP	blood pressure
BPD	Borderline personality disorder
BPSD	behavioural and psychological symptoms of dementia
BuChE	butyrylcholinesterase
CAMS	Childhood Anxiety Multimodal Study
CATIE	Clinical Antipsychosis Trials of Intervention Effectiveness
CBT	cognitive behavioural therapy
CDRS	Children's Depression Rating Scale
CDR-SB	Clinical Dementia Rating Scale – Sums of Boxes
CDRS-R	Children's Depression Rating Scale-Revised
CGAS	Children's Global Assessment Scale
CGI	Clinical Global Impression
CI	confidence interval
CIBIC-plus	Clinician's Interview-Based Impression of Change plus caregiver input
CIGH	clozapine-induced GI hypomotility
CIWA-Ar	Clinical Institute Withdrawal Assessment of Alcohol Scale Revised
CK	creatine kinase
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNS	central nervous system
COCP	combined oral contraceptive pill
COMT	catechol-O-methyltransferase
COPD	chronic obstructive pulmonary disease
COWS	Clinical Opiate Withdrawal Scale
CQC	Care Quality Commission
CrCl	creatinine clearance
CRLTA	clozapine-related life-threatening agranulocytosis
CRP	C-reactive protein
CTO	Community Treatment Order
CUtLASS	Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study
CVD	cardiovascular disease
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale
CYP	cytochrome P450
DAI	Drug Attitude Inventory
DBM	dibenzoylmethane
DBT	dialectical behaviour therapy
DEXA	dual-energy x-ray absorptiometry
DHA	docosahexaenoic acid
DHEA	dehydroepiandrosterone
DIVA-5	Diagnostic Interview for ADHD in Adults
DLB	dementia with Lewy bodies
DMDD	disruptive mood dysregulation disorder
DMq	dextromethorphan and low-dose quinidine
DOACs	direct-acting oral anticoagulants
DoLS	Deprivation of Liberty Safeguards

DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition
DVLA	Driver and Vehicle Licensing Agency
ECG	electrocardiogram
ECT	electroconvulsive therapy
EEG	electroencephalogram
eGFR	estimated glomerular filtration rate
EMDR	eye movement desensitisation and reprocessing
EOSS	early-onset schizophrenia spectrum
EPA	eicosapentaenoic acid
EPS	extrapyramidal symptoms
EPSE	extrapyramidal side effect
ER	extended release
ERK	extracellular signal-regulated kinase
ES	effect size
EU	European Union
FBC	full blood count
FDA	Food and Drug Administration
FGA	first-generation antipsychotic
FPG	fasting plasma glucose
FRAMES principles	feedback, responsibility, advice, menu, empathy, self-efficacy
FSH	follicle-stimulating hormone
FTI	Fatal Toxicity Index
GABA	gamma-aminobutyric acid
GAD	generalised anxiety disorder
GASS	Glasgow Antipsychotic Side-effect Scale
GBL	gamma-butyrolactone
G-CSF	granulocyte colony-stimulating factor
GERD	gastro-esophageal reflux disease
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GHB	gamma-hydroxybutyrate
GHB/GBL	gamma-hydroxybutyrate/gamma-butyrolactone
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GP	general practitioner
GRDS	gastric reduction duodenal switch
GSM	genitourinary symptoms of menopause
HAD	HIV-associated dementia
HAM-D	Hamilton Depression Rating Scale
HAND	HIV-assocated neurocognitive disorders
HbA_{1c}	glycated haemoglobin
HCl	hydrogen chloride
HD	Huntington's disease
HDL	high-density lipoprotein
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HLA	human lymphocyte antigen
HPA	hypothalamic–pituitary–adrenal
HR	hazard ratio
HRT	hormone replacement therapy
IADL	instrumental activities of daily living
ICD-10	*International Classification of Diseases 10*
ICH	intracranial/intracerebral haemorrhage
IGSLI	International Study Group on Lithium
IHD	ischaemic heart disease
IM	intramuscular
INR	international normalised ratio
IR	immediate release

ISBD	International Society for Bipolar Disorders
ISTSS	International Society for Traumatic Stress Studies
IV	intravenous
Kiddie-SADS	Kiddie-Schedule for Affective Disorders and Schizophrenia
LAI	long-acting injection
LC-MS	liquid chromatography and mass spectrometry
LD	learning disabilities
LDL	low-density lipoprotein
LFT	liver function test
LGIB	lower gastrointestinal bleeding
LMP	last menstrual period
MADRS	Montgomery–Asberg Depression Rating Scale
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
MARS	Medication Adherence Rating Scale
MASC	Multidimensional Anxiety Scale for Children
MCA	Mental Capacity Act
MCI	mild cognitive impairment
MDD	major depressive disorder
MDMA	3,4-methylenedioxymethamphetamine
MDRD	Modification of Diet in Renal Disease
MDT	multidisciplinary team
MFQ	Mood and Feelings Questionnaire
MHA	Mental Health Act
MHRA	Medicines and Healthcare products Regulatory Authority
MI	myocardial infarction
MMSE	Mini Mental State Examination
MND	mild neurocognitive disorder
MoCA	Montreal Cognitive Assessment
MR	modified release
MS	mood stabilisers/multiple sclerosis
MSM	men who have sex with men
NAPLS	North American Prodromal Longitudinal Studies
NaSSA	noradrenergic and specific serotonergic antidepressant
NbN	neuroscience-based nomenclature
NEET	not in education, employment or education
NICE	National Institute for Health and Care Excellence
NIMH	National Institute of Mental Health
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptor
NMS	neuroleptic malignant syndrome
NNH	number needed to harm
NNT	number needed to treat
NPIS	National Poisons Information Service
NPS	new psychoactive substances
NPV	negative predictive value
NRT	nicotine replacement therapy
NSAID	non-steroidal anti-inflammatory drug
OCD	obsessive compulsive disorder
od	once daily
OGTT	oral glucose tolerance test
on	at night
OOWS	Objective Opiate Withdrawal Scale
OR	odds ratio
OST	opioid substitution treatment

PAIN	Peri-operative Pain and Addiction Interdisciplinary Network
PANDAS	paediatric autoimmune neuropsychiatric disorder associated with *Streptococcus*
PANS	paediatric acute-onset neuropsychiatric syndrome
PANSS	Positive and Negative Syndrome Scale
PAWS	post-acute withdrawal syndrome
PBA	pseudobulbar affect
PD	Parkinson's disease
PDSS	post-injection delirium sedation syndrome
PE	pulmonary embolism
PET	positron emission tomography
PG	propylene glycol
P-gp	P-glycoprotein
PHQ-9	Patient Health Questionnaire-9
PLWH	people living with HIV
PMDD	premenstrual dysphoric disorder
PMR	postmortem redistribution
PMS	premenstrual syndrome
po	by mouth
POI	premature ovarian insufficiency
PORT	Program of Rehabilitation and Therapy
PP1M	paliperidone long-acting injection 1-monthly
PP3M	paliperidone long-acting injection 3-monthly
PPH	postpartum haemorrhage
PPI	proton pump inhibitor
PPV	positive predictive value
prn	as required
PSSD	post-SSRI sexual dysfunction
PT	prothrombin time
PTSD	post-traumatic stress disorder
PUFA	polyunsaturated fatty acid
PWE	people with epilepsy
RANZCP	Royal Australian and New Zealand College of Psychiatrists
RC	Responsible Clinician
RCADS	Revised Children's Anxiety and Depression Scale
RCT	randomised controlled trial
REM	rapid eye movement
RID	relative infant dose
RIMA	reversible inhibitor of monoamine oxidase A
RLAI	risperidone long-acting injection
ROMI	Rating of Medication Influences
RR	respiratory rate/risk ratio
RRBI	restricted repetitive behaviours and interests
RT	rapid tranquillisation
RTA	road traffic accident
rTMS	repetitive transcranial magnetic stimulation
RUPP	Research Units on Paediatric Psychopharmacology
RYGB	Roux-en-Y gastric bypass
SADQ	Severity of Alcohol Dependence Questionnaire
SAWS	Short Alcohol Withdrawal Scale
SC	subcutaneous
SCARED	Screen for Child Anxiety and Related Emotional Disorders
SCRA	synthetic cannabinoid receptor agonist
SD	sexual dysfunction
SERM	selective oestrogen receptor modulators
SERT	serotonin receptor

SGA	second-generation antipsychotic
SIADH	syndrome of inappropriate secretion of antidiuretic hormone
SIB	Severe Impairment Battery
SJW	St John's wort
SNRI	serotonin–noradrenaline reuptake inhibitor
SOAD	Second Opinion Appointed Doctor
SPC	Summary of Product Characteristics
SROM	slow-release oral morphine
SSRI	selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
STOP-PD II	Study of the Pharmacotherapy of Psychotic Depression II
SUD	stimulant use disorder
TADS	Treatment of Adolescents with Depression Study
TCA	tricyclic antidepressant
TD	tardive dyskinesia
tDCS	transcranial direct current stimulation
TDM	therapeutic drug monitoring
TdP	torsades de pointes
tds	three times a day
TF-CBT	trauma-focused cognitive behavioural therapy
TFT	thyroid function test
TIA	transient ischaemic attack
tMS	transcranial magnetic stimulation
TORDIA	Treatment of Resistant Depression in Adolescents
TRBD	treatment-resistant bipolar disorder
TRD	treatment-resistant depression
TREC	Tranquilização Rápida-Ensaio Clínico [Rapid Tranquillisation Clinical Trial]
TRS	treatment-resistant schizophrenia
TS	Tourette syndrome
U&Es	urea and electrolytes
UDP	uridine diphosphate
UGT	UDP-glucuronosyltransferase
UGIB	upper gastrointestinal bleeding
UGT	UDP-glucuronosyltransferase
UKTIS	UK Teratology Information Service
VaD	vascular dementia
VG	vegetable glycerine
VHR	Vienna High Risk
VMAT-2	vesicular monoamine transporter 2
VNS	vagal nerve stimulation
VTE	venous thromboembolism
WBC	white blood cell
WCC	white cell count
WHO	World Health Organization
YMRS	Young Mania Rating Scale
ZA	zuclopenthixol acetate

Chapter 1

Schizophrenia and related psychoses

ANTIPSYCHOTIC DRUGS

General introduction

Classification of antipsychotics

Before the 1990s, antipsychotics (or major tranquillisers as they were then known) were classified according to their chemistry. The first antipsychotic, chlorpromazine, was a phenothiazine compound – a tricyclic structure incorporating a nitrogen and a sulphur atom. Further phenothiazines were generated and marketed, as were chemically similar thioxanthenes such as flupentixol. Later, entirely different chemical structures were developed according to pharmacological paradigms. These included butyrophenones (haloperidol), diphenylbutylpiperidines (pimozide) and substituted benzamides (sulpiride, amisulpride).

Chemical classification remains useful but is rendered somewhat redundant by the broad range of chemical entities now available and by the absence of any clear structure–activity relationships for newer drugs. The chemistry of some older drugs does relate to their propensity to cause movement disorders. Piperazine phenothiazines (e.g. fluphenazine, trifluoperazine), butyrophenones and thioxanthenes are most likely to cause extrapyramidal effects, while piperidine phenothiazines (e.g. pipotiazine) and benzamides are the least likely. Aliphatic phenothiazines (e.g. chlorpromazine) and diphenylbutylpiperidines (pimozide) are perhaps somewhere in between.

Relative liability for inducing extrapyramidal side effects (EPSEs) was originally the primary factor behind the typical/atypical classification. Clozapine had long been known as an atypical antipsychotic on the basis of its low liability to cause EPSEs and its failure in animal-based antipsychotic screening tests. Its remarketing in 1990 signalled the beginning of a series of new medications, all of which were introduced with claims (to varying degrees of accuracy) of 'atypicality'. Of these medications, perhaps only clozapine, and possibly quetiapine, is completely atypical, seemingly having a

The Maudsley® Prescribing Guidelines in Psychiatry, Fifteenth Edition. David M. Taylor, Thomas R. E. Barnes and Allan H. Young.

very low or zero liability for extrapyramidal symptoms (EPS). Others show dose-related effects, although, unlike with typical drugs, therapeutic activity can usually be achieved without EPSEs. This is possibly the real distinction between typical and atypical drugs: the ease with which a dose can be chosen within the licensed dosage range that is effective but does not cause EPSEs (for example, compare haloperidol with olanzapine).

The typical/atypical dichotomy does not lend itself well to classification of antipsychotics in the middle ground of EPSE liability. Thioridazine was widely described as atypical in the 1980s but is a 'conventional' phenothiazine. Sulpiride was marketed as an atypical but is often classified as typical. Risperidone, at its maximum dose of 16mg/day, is just about as 'typical' as a drug can be. Alongside these difficulties is the fact that there is nothing either pharmacologically or chemically which clearly binds these so-called atypicals together as a group, save perhaps a general but not universal finding of preference for D2 receptors outside the striatum. Nor are atypicals characterised by improved efficacy over older drugs (clozapine and one or two others excepted) or the absence of hyperprolactinaemia (which is usually worse with risperidone, paliperidone and amisulpride than with typical drugs). Lastly, some more recently introduced agents (e.g. pimavanserin, xanomeline) have antipsychotic activity and do not cause EPS but have almost nothing in common with other atypicals in respect to chemistry, pharmacology or adverse-effect profile.

In an attempt to get round some of these problems, typicals and atypicals were reclassified as first- or second-generation antipsychotics (FGA/SGA). All drugs introduced since 1990 are classified as SGAs (i.e. all atypicals) but the new nomenclature dispenses with any connotations regarding atypicality, whatever that may mean. However, the FGA/SGA classification remains problematic because neither group is defined by anything other than time of introduction – hardly the most sophisticated pharmacological classification system. Perhaps more importantly, date of introduction is often wildly distant from date of first synthesis. Clozapine is one of the oldest antipsychotics (synthesised in 1959) while olanzapine is hardly in its first flush of youth, having first been patented in 1971. These two drugs are of course SGAs, apparently the most modern of antipsychotics.

In this edition of the *Maudsley Prescribing Guidelines*, we conserve the FGA/SGA distinction more because of convention than some scientific basis. Also, we feel that most people know which drugs belong to each group – it thus serves as a useful shorthand. However, it is clearly more sensible to consider the properties of *individual* antipsychotics when choosing drugs to prescribe or in discussions with patients and carers. With this in mind, the use of Neuroscience-based Nomenclature (NbN)[1] – a naming system that reflects pharmacological activity – is strongly recommended.

Choosing an antipsychotic

In the UK, the National Institute for Health and Care Excellence (NICE) guideline for medicines adherence[2] recommends that patients should be as involved as possible in decisions about the choice of medicines that are prescribed for them, and that clinicians should be aware that illness beliefs and beliefs about medicines influence adherence. Consistent with this general advice that covers all healthcare, the NICE guideline for schizophrenia emphasises the importance of patient choice rather than specifically recommending a class or individual antipsychotic as first-line treatment.[3]

Antipsychotics are effective in both the acute and maintenance treatment of schizophrenia and other psychotic disorders. They differ in their pharmacology, pharmacokinetics, overall efficacy/effectiveness and tolerability, and, perhaps more importantly, response and tolerability differ between patients. This variability of individual response means that there is no clear first-line antipsychotic medication that is preferable for all.

Relative efficacy

After the publication of the independent CATIE[4] and CUtLASS[5] studies, the World Psychiatric Association reviewed the evidence relating to the relative efficacy of 51 FGAs and 11 SGAs and concluded that, if differences in EPS could be minimised (by careful dosing) and anticholinergic use avoided, there was no convincing evidence to support any advantage for SGAs over FGAs.[6] As a class, SGAs may have a lower propensity for EPS and tardive dyskinesia (TD),[7] but this was somewhat offset by a higher propensity to cause metabolic adverse effects. A meta-analysis of antipsychotic medications for first-episode psychosis[8] found few differences between FGAs and SGAs as groups of drugs but minor advantages for olanzapine and amisulpride individually. A later network meta-analysis of first-episode studies found small efficacy advantages for olanzapine and amisulpride and overall poor performance for haloperidol.[9]

When individual non-clozapine SGAs are compared, summary data suggest that olanzapine is marginally more effective than aripiprazole, risperidone, quetiapine and ziprasidone, and that risperidone has a minor advantage over quetiapine and ziprasidone.[10] FGA-controlled trials also suggest an advantage for olanzapine, risperidone and amisulpride over older drugs.[11,12] A network meta-analysis[13] broadly confirmed these findings, ranking amisulpride second behind clozapine and olanzapine third. These three drugs were the only ones to show clear efficacy advantages over haloperidol. The magnitude of differences was again small (but potentially substantial enough to be clinically important)[13] and must be weighed against the very different adverse effect profiles associated with individual antipsychotics. A 2019 network meta-analysis of 32 antipsychotics[14] ranked amisulpride as the most effective drug for positive symptoms and clozapine as the best for both negative symptoms and overall symptom improvement. Olanzapine and risperidone were also highly ranked for positive symptom response. The greatest (beneficial) effect on depressive symptoms was seen with sulpiride, clozapine, amisulpride, olanzapine and the dopamine partial agonists, perhaps reflecting the relative absence of neuroleptic-induced dysphoria common to most FGAs.[15] In the longer term, olanzapine may have advantages over some other antipsychotics.[16] There was a tendency for more recently introduced drugs to have a lower estimated efficacy – a phenomenon that derives from the substantial increase in placebo response since 1970.[17]

Clozapine is clearly the drug of choice in refractory schizophrenia,[18] although bizarrely, this is not a universal finding,[19] probably because of the biased nature and quality of many active–comparator trials.[20,21]

Both FGAs and SGAs are associated with a number of adverse effects. These include weight gain, dyslipidaemia, increases in plasma glucose/diabetes,[22,23] hyperprolactinaemia, hip fracture,[24] sexual dysfunction, EPS including neuroleptic malignant syndrome,[25] anticholinergic effects, venous thromboembolism (VTE),[26] sedation and postural hypotension. The exact profile is drug specific (see individual sections on

specific adverse effects), although comparative data are not robust[27] (see large-scale meta-analyses[13,28] for rankings of some adverse-effect risks).

Adverse effects are a common reason for treatment discontinuation,[29] particularly when efficacy is poor.[13] Patients do not always spontaneously report adverse effects, however,[30] and psychiatrists' views of the prevalence and importance of adverse effects differ markedly from patient experience.[31] Systematic enquiry, together with a physical examination and appropriate biochemical tests, is the only way accurately to assess their presence and severity or perceived severity. Patient-completed checklists such as the Glasgow Antipsychotic Side-effect Scale (GASS)[32] can be a useful first step in this process. The clinician-completed Antipsychotic Non-Neurological Side-Effects Rating Scale facilitates more detailed and comprehensive assessment.[33]

Non-adherence to antipsychotic treatment is common and here the guaranteed medication delivery associated with depot/long-acting injectable antipsychotic preparations (LAIs) is unequivocally advantageous. In comparison with oral antipsychotics, there is strong evidence that depots are associated with a reduced risk of relapse and rehospitalisation,[34–36] although randomised controlled trials (RCTs) do not always reflect this difference.[37] Any logical assessment of the benefits of LAIs and the damage caused by relapse would conclude that LAIs should be first-line treatments, rather than reserved for those who have already relapsed on oral medication. Moreover, the wider use of SGA LAIs has to some extent changed the image of depots, which were sometimes perceived as punishments for miscreant patients. Their tolerability advantage probably relates partly to the better definition of their therapeutic dose range, meaning that the optimal dose is more likely to be prescribed (compare aripiprazole, with a licensed dose 300mg or 400mg/month, with flupentixol, which has a licensed dose in the UK of 50mg every 4 weeks to 400mg/week). The optimal dose of flupentixol is around 40mg every 2 weeks[28] – just 5% of the maximum allowed.

As already mentioned, for patients whose symptoms have not responded sufficiently to adequate, sequential trials of two or more antipsychotic drugs, clozapine is the most effective treatment.[38–40] Its use in these circumstances is recommended by NICE[3] and probably every schizophrenia guideline besides. The biological basis for the superior efficacy of clozapine is uncertain.[41] Olanzapine should probably be one of the two drugs used before clozapine.[10,42] A case might also be made for a trial of amisulpride: it has a uniformly high ranking in meta-analyses and one trial found continuation with amisulpride to be as effective as switching to olanzapine.[43] This same trial also suggested clozapine might be best placed as the second drug used, given that switching provided no benefit over continuing with the first prescribed drug.

This chapter covers the treatment of schizophrenia with antipsychotic drugs, the relative adverse effect profile of these drugs and how adverse effects can be managed.

References

1. Zohar J, et al. Neuroscience-based Nomenclature (NbN): a call for action. *World J Biol Psychiatry* 2016; **17**:318–320.
2. National Institute for Health and Care Excellence. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. Clinical guideline [CG76]. 2009 (last updated March 2019, last checked December 2024); https://www.nice.org.uk/Guidance/CG76.
3. National Institute for Health and Care Excellence. Psychosis and schizophrenia in adults: prevention and management. Clinical guideline [CG178]. 2014 (last checked November 2024); https://www.nice.org.uk/guidance/cg178.
4. Lieberman JA, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005; **353**:1209–1223.
5. Jones PB, et al. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Arch Gen Psychiatry* 2006; **63**:1079–1087.
6. Tandon R, et al. World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. *Schizophr Res* 2008; **100**:20–38.
7. Tarsy D, et al. Epidemiology of tardive dyskinesia before and during the era of modern antipsychotic drugs. *Handb Clin Neurol* 2011; **100**:601–616.
8. Zhang JP, et al. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. *Int J Neuropsychopharmacol* 2013; **16**:1205–1218.
9. Zhu Y, et al. Antipsychotic drugs for the acute treatment of patients with a first episode of schizophrenia: a systematic review with pairwise and network meta-analyses. *Lancet Psychiatry*; **4**:694–705.
10. Leucht S, et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *Am J Psychiatry* 2009; **166**:152–163.
11. Davis JM, et al. A meta-analysis of the efficacy of second-generation antipsychotics. *Archives of General Psychiatry* 2003; **60**:553–564.
12. Leucht S, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 2009; **373**:31–41.
13. Leucht S, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 2013; **382**:951–962.
14. Huhn M, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet* 2019; **394**:939–951.
15. Voruganti L, et al. Neuroleptic dysphoria: towards a new synthesis. *Psychopharmacology (Berl)* 2004; **171**:121–132.
16. Leucht S, et al. Long-term efficacy of antipsychotic drugs in initially acutely ill adults with schizophrenia: systematic review and network meta-analysis. *World Psychiatry* 2023; **22**:315–324.
17. Leucht S, et al. Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, Bayesian meta-analysis, and meta-regression of efficacy predictors. *Am J Psychiatry* 2017; **174**:927–942.
18. Siskind D, et al. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. *Br J Psychiatry* 2016; **209**:385–392.
19. Samara MT, et al. Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: a network meta-analysis. *JAMA Psychiatry* 2016; **73**:199–210.
20. Taylor DM. Clozapine for treatment-resistant schizophrenia: still the gold standard? *CNS Drugs* 2017; **31**:177–180.
21. Kane JM, et al. The role of clozapine in treatment-resistant schizophrenia. *JAMA Psychiatry* 2016; **73**:187–188.
22. Manu P, et al. Prediabetes in patients treated with antipsychotic drugs. *J Clin Psychiatry* 2012; **73**:460–466.
23. Rummel-Kluge C, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Schizophr Res* 2010; **123**:225–233.
24. Sorensen HJ, et al. Schizophrenia, antipsychotics and risk of hip fracture: a population-based analysis. *Eur Neuropsychopharmacol* 2013; **23**:872–878.
25. Trollor JN, et al. Comparison of neuroleptic malignant syndrome induced by first- and second-generation antipsychotics. *Br J Psychiatry* 2012; **201**:52–56.
26. Masopust J, et al. Risk of venous thromboembolism during treatment with antipsychotic agents. *Psychiatry Clin Neurosci* 2012; **66**:541–552.
27. Pope A, et al. Assessment of adverse effects in clinical studies of antipsychotic medication: survey of methods used. *Br J Psychiatry* 2010; **197**:67–72.
28. Bailey L, et al. Estimating the optimal dose of flupentixol decanoate in the maintenance treatment of schizophrenia: a systematic review of the literature. *Psychopharmacology (Berl)* 2019; **236**:3081–3092.
29. Falkai P. Limitations of current therapies: why do patients switch therapies? *Eur Neuropsychopharmacol* 2008; **18** Suppl 3:S135–S139.
30. Yusufi B, et al. Prevalence and nature of side effects during clozapine maintenance treatment and the relationship with clozapine dose and plasma concentration. *Int Clin Psychopharmacol* 2007; **22**:238–243.
31. Day JC, et al. A comparison of patients' and prescribers' beliefs about neuroleptic side-effects: prevalence, distress and causation. *Acta Psychiatr Scand* 1998; **97**:93–97.
32. Waddell L, et al. A new self-rating scale for detecting atypical or second-generation antipsychotic side effects. *J Psychopharmacol* 2008; **22**:238–243.
33. Ohlsen RI, et al. Interrater reliability of the Antipsychotic Non-Neurological Side-Effects Rating Scale measured in patients treated with clozapine. *J Psychopharmacol* 2008; **22**:323–329.

34. Tiihonen J, et al. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. *BMJ* 2006; **333**:224.
35. Leucht C, et al. Oral versus depot antipsychotic drugs for schizophrenia—a critical systematic review and meta-analysis of randomised long-term trials. *Schizophr Res* 2011; **127**:83–92.
36. Leucht S, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet* 2012; **379**:2063–2071.
37. Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral and long-acting injectable antipsychotics for the maintenance treatment of adults with schizophrenia: a systematic review and network meta-analysis. *Lancet* 2022; **399**:824–836.
38. Kane J, et al. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988; **45**:789–796.
39. McEvoy JP, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry* 2006; **163**:600–610.
40. Lewis SW, et al. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. *Schizophr Bull* 2006; **32**:715–723.
41. Stone JM, et al. Review: the biological basis of antipsychotic response in schizophrenia. *J Psychopharmacol* 2010; **24**:953–964.
42. Agid O, et al. An algorithm-based approach to first-episode schizophrenia: response rates over 3 prospective antipsychotic trials with a retrospective data analysis. *J Clin Psychiatry* 2011; **72**:1439–1444.
43. Kahn RS, et al. Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE): a three-phase switching study. *Lancet Psychiatry* 2018; **5**:797–807.