The Maudsley®

Prescribing Guidelines in Psychiatry

14TH 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 in Psychiatry

14th 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 2021

Registered Office(s)
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

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

A catalogue record for this book is available from the Library of Congress

Paperback ISBN: 9781119772224; ePDF ISBN: 9781119772248; epub ISBN: 9781119772231

Cover design by Wiley

Set in 10/12pt Sabon by Integra Software Services, Pondicherry, India

10 9 8 7 6 5 4 3 2 1

Contents

Preface

This 14th edition of *The Guidelines* has been written under extraordinary circumstances: the coronavirus pandemic. This global phenomenon has radically altered the lives and working practices of billions of people, and most of us are now familiar, either personally or vicariously, with the experience of the serious physical illness that is associated with COVID-19.

Those working in healthcare have been particularly grievously affected, caring for those made ill by the disease while risking infection themselves. In this environment, the writing of a book has an extremely low priority, if any at all. It is in this context that I give boundless and sincere thanks to all those who have contributed to this edition of *The Guidelines* under such challenging conditions.

Of course, mental health problems have not gone away during the pandemic, and the optimal treatment of mental illness remains a vital imperative. This objective will be all the more critical as we come to deal with the mental health consequences of the pandemic.

This edition of *The Guidelines* has been thoroughly updated to include influential research published since 2017 and all major psychotropic drugs introduced since that time. This edition is also somewhat expanded by the inclusion of new sections on such subjects as the management of agitated delirium, psychotropics at the end of life, intravenous psychotropic formulations, intramuscular clozapine and weekly oral penfluridol. As with previous editions, the 14th edition is written with the intention of having worldwide utility, but it retains its mild emphasis on UK practice.

I would like to pay special tribute to Siobhan Gee for her numerous meticulously prepared contributions on the use of clozapine, Mark Horowitz for his evidence-based and patient-centred guidance on discontinuation of psychotropics, Delia Bishara for her near single-handed production of the chapter on older adults, and Ian Osborne for his contributions on an exceptionally varied range of subjects. Emily Finch deserves particular recognition for organising the writing of the chapter on addictions for the last ten editions of *The Guidelines*. Lastly, I would like to thank my assistant Ivana Clark for managing the production of this edition with patience and an unparalleled attention to detail.

David M. Taylor
London
March 2021

Acknowledgments

The following have contributed to the 14th edition of *The Maudsley® Prescribing Guidelines in Psychiatry*.

Alice Debelle
Andrea Danese
Andrew Wilcock
Annabel Price
Anne Connolly
Bruce Clark
Claire Wilson
Colin Drummond
Daniel Harwood
David Mirfin
Deborah Robson
Delia Bishara
Derek Tracy
Ebenezer Oloyede
Elizabeth Naomi Smith
Emily Finch
Emmert Roberts
Eromona Whiskey
Francis Keaney
Frank Besag
Gabriel Ruane
Georgina Boon
Hubertus Himmerich
Ian Osborne
Irene Guerrini
Iris Rathwell
Ivana Clark
James Stone
Jane Marshall
Janet Treasure
Jemma Theivendran
Jonathan Rogers
Justin Sauer
Kalliopi Vallianatou
Kwame Peprah
Louise Howard
Luke Baker
Luke Jelen
Marinos Kyriakopoulos
Mark Horowitz
Max Henderson
Mike Kelleher
Nicola Funnell
Nicola Kalk
Nilou Nourishad
Oluwakemi Oduniyi
Paramala Santosh
Paul Gringras
Paul Moran
Petrina Douglas-Hall
Sameer Jauhar
Shubhra Mace
Siobhan Gee
Sotiris Posporelis
Stephanie J Lewis
Stephen Barclay

Notes on using *The Maudsley® Prescribing Guidelines in Psychiatry*

The main aim of *The Guidelines* is to provide clinicians with practically useful advice on the prescribing of psychotropic agents in both commonly and less commonly encountered clinical situations. The advice contained in this handbook is based on a combination of literature review, clinical experience and expert contribution. We do not claim that this advice is necessarily 'correct' or that it deserves greater prominence than the guidance provided by other professional bodies or special interest groups. We hope, however, to have provided guidance that helps to assure the safe, effective and economic use of medicines in psychiatry. We hope also to have made clear precisely the sources of information used to inform the guidance given. Please note that many of the recommendations provided here go beyond the licensed or labelled indications of many drugs, both in the UK and elsewhere. Note also that, while we have endeavoured to make sure all quoted doses are correct, clinicians should always consult statutory texts before prescribing. Users of *The Guidelines* should also bear in mind that the contents of this handbook are based on information available to us in March 2021. Much of the advice contained here will become out-dated as more research is conducted and published.

No liability is accepted for any injury, loss or damage, however caused.

Notes on inclusion of drugs

The Guidelines are used in many other countries outside the UK. With this in mind, we have included in this edition those drugs in widespread use throughout the Western world in March 2021. These include drugs not marketed in the UK, such as brexpiprazole, desvenlafaxine, pimavanserin and vilazodone, amongst several others. Many older drugs or those not widely available (e.g. levomepromazine, pericyazine, maprotiline, zotepine, oral loxapine, etc.) are either only briefly mentioned or not included on the basis that these drugs are not in widespread use at the time of writing.

Contributors' Conflict of Interest

Most 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 the 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

AACAP	American Academy of Child and Adolescent Psychiatry
ACE	angiotensin-converting enzyme
ACh	acetylcholine
AChE	acetylcholinesterase
AChE-I	acetylcholinesterase inhibitor
ACR	albumin: creatinine ratio
AD	Alzheimer's disease
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 reaction
AF	atrial fibrillation
AIDS	acquired immune deficiency syndrome
AIMS	Abnormal Involuntary Movement Scale
ALP	alkaline phosphatase
ALT	alanine transaminase/ aminotransferase
ANC	absolute neutrophil count
ANNSERS	Antipsychotic Non-Neurological Side-Effects Rating Scale
APA	American Psychological Association
ARB	angiotensin II receptor blocker
ASD	autism spectrum disorders
ASEX	Arizona Sexual Experience Scale
AST	aspartate aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
BAC	blood alcohol concentration
BAP	British Association for Psychopharmacology
BBB	blood–brain barrier
bd	*bis die* (twice a day)
BDD	body dysmorphic disorder
BDI	Beck Depression Inventory
BDNF	brain-derived neurotrophic factor
BED	binge eating disorder
BEN	benign ethnic neutropenia
BMI	body mass index
BN	bulimia nervosa
BP	blood pressure
BPD	borderline personality disorder
BPSD	behavioural and psychological symptoms of dementia
BuChE	butyrylcholinesterase
CAM	Confusion Assessment Method
CAMS	Childhood Anxiety Multimodal Study
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CBT	cognitive behavioural therapy

CBZ	carbamazepine
CDRS	Children's Depression Rating Scale
CDT	carbohydrate-deficient transferrin
CES-D	Centre for Epidemiological Studies Depression scale
CGAS	Children's Global Assessment Scale
CGI	Clinical Global Impression scales
CI	confidence interval
CIBIC-Plus	Clinician's Interview-Based Impression of Change
CIGH	clozapine-induced gastrointestinal 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
COMT	catechol-O-methyltransferase
COPD	chronic obstructive pulmonary disease
COX	cyclo-oxygenase
CPK	creatinine phosphokinase
CPP	child–parent psychotherapy
CPSS	Child PTSD Symptom Scale
CrCl	creatinine clearance
CREB	cAMP response element-binding protein
CRP	C-reactive protein
CUtLASS	Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study
CVA	cerebrovascular accident
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale
CYP	cytochrome P
DAI	drug attitude inventory
DESS	Discontinuation–Emergent Signs and Symptoms scale
DEXA	dual-energy X-ray absorptiometry
DHEA	dehydroepiandrosterone
DIVA	Diagnostic Interview for DSM-IV ADHD
DLB	dementia with Lewy bodies
DMDD	disruptive mood dysregulation disorder
DOAC	direct-acting oral anticoagulant
DoLS	Deprivation of Liberty Safeguards
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
DVLA	Driver and Vehicle Licensing Agency
EAD	early after depolarisation
ECG	electrocardiogram
ECT	electroconvulsive therapy
EDTA	ethylenediaminetetraacetic acid
EEG	electroencephalogram
eGFR	estimated glomerular filtration rate
EMDR	eye movement desensitisation and reprocessing
EOSS	early-onset schizophrenia-spectrum
EPA	eicosapentanoic acid
EPS	extrapyramidal symptoms
ER	extended release
ERK	extracellular signal-regulated kinase
ERP	exposure and response prevention
ES	effect size
ESR	erythrocyte sedimentation rate
FAST	functional assessment staging
FBC	full blood count
FDA	Food and Drug Administration (USA)
FGA	first-generation antipsychotic
FPG	fasting plasma glucose
FTI	Fatal Toxicity Index
GABA	γ-aminobutyric acid
GAD	generalised anxiety disorder
GASS	Glasgow Antipsychotic Side-effect Scale
GBL	gamma-butyrolactone
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GGT	γ-glutamyl transferase

GHB	γ-hydroxybutyrate
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
GSK3	glycogen synthase kinase 3
HADS	Hospital Anxiety and Depression Scale
HAMA	Hamilton Anxiety Rating Scale
HAND	HIV-associated neurocognitive disorders
HD	Huntington's disease
HDL	high-density lipoprotein
HDRS	Hamilton Depression Rating Scale
HIV	human immunodeficiency virus
5-HMT	5-hydroxy-methyl-tolterodine
HPA	hypothalamic-pituitary-adrenal
HR	hazard ratio
IADL	instrumental activities of daily living
ICD	International Classification of Diseases
ICH	intracerebral haemorrhage
IFG	impaired fasting glucose
IG	intra-gastric
IJ	intra-jejunal
IM	intramuscular
IMCA	independent mental capacity advocate
IMHP	intramuscular high potency
INR	international normalised ratio
IR	immediate release
IV	intravenous
IVHP	intravenous high potency
Kiddie-SADS	Kiddie-Schedule for Affective Disorders and Schizophrenia
LAI	long-acting injection
LD	learning disability
LDL	low-density lipoprotein
LFTs	liver function tests
LGIB	lower gastrointestinal bleeding
LSD	lysergic acid diethylamide
MADRS	Montgomery-Asberg Depression Rating Scale
mane	morning
MAOI	monoamine oxidase inhibitor
MARS	Medication Adherence Rating Scale
MASC	Multidimensional Anxiety Scale for Children
MCA	Mental Capacity Act
MCI	mild cognitive impairment
MDA	3,4-methylenedioxyamphetamine
MDMA	3,4-methylenedioxymethamphetamine
MDRD	Modification of Diet in Renal Disease
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	myocardial infarction
MMSE	Mini Mental State Examination
MR	modified release
MS	mood stabilisers/multiple sclerosis
NAS	neonatal abstinence syndrome
NICE	National Institute for Health and Care Excellence
NMDA	N-methyl-D-aspartate
NMS	neuroleptic malignant syndrome
NNH	number needed to harm
NNT	number needed to treat
nocte	at night
NPI	neuropsychiatric inventory
NRT	nicotine replacement therapy
NSAID	non-steroidal anti-inflammatory drug
NVC	neurovascular coupling
OCD	obsessive compulsive disorder
od	*omni die* (once a day)
OD	overdose
OGTT	oral glucose tolerance test
OOWS	Objective Opiate Withdrawal Scale
OST	opioid substitution treatment
PANDAS	Paediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus
PANS	Paediatric Acute-onset Neuropsychiatric Syndrome
PANSS	Positive and Negative Syndrome Scale
PBA	pseudobulbar affect
PCP	phencyclidine
PD	Parkinson's disease

PDD	pervasive developmental disorders
PDD-NOS	pervasive developmental disorders not otherwise specified
P-gp	P-glycoprotein
PHQ-9	Patient Health Questionnaire-9
PICU	psychiatric intensive care unit
PLC	pathological laughter and crying
PLWH	people living with HIV
PMR	post-mortem redistribution
po	*per os* (by mouth)
POMH-UK	Prescribing Observatory for Mental Health
PPH	post-partum haemorrhage
PPI	proton pump inhibitor
prn	*pro re nata* (as required)
PT	prothrombin time
PTSD	post-traumatic stress disorder
PWE	people with epilepsy
qds	*quarter die sumendum* (four times a day)
QTc	QT interval adjusted for heart rate
RC	responsible clinician
RCADS	Revised Children's Anxiety and Depression Scale
RCT	randomised controlled trial
RID	relative infant dose
RIMA	reversible inhibitor of monoamine oxidase A
RLAI	risperidone long-acting injection
ROMI	Rating of Medication Influences scale
RPG	random plasma glucose
RR	relative risk
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
SCARED	Screen for Child Anxiety and Related Emotional Disorders
SCIRS	Severe Cognitive Impairment Rating Scale
SCRA	synthetic cannabinoid receptor agonist
SGA	second-generation antipsychotics
SIADH	syndrome of inappropriate antidiuretic hormone
SIB	severe impairment battery
SJW	St. John's wort
SLE	systemic lupus erythematosus
SNRI	serotonin–noradrenaline reuptake inhibitor
SOAD	second opinion appointed doctor
SPC	summary of product characteristics
SPECT	single photon emission computed tomography
SROM	slow release oral morphine
SS	steady state
SSRI	selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression programme
STS	selegiline transdermal system
TADS	Treatment of Adolescents with Depression Study
TCA	tricyclic antidepressant
TD	tardive dyskinesia
tDCS	transcranial direct current stimulation
TDP	torsades de pointes
tds	*ter die sumendum* (three times a day)
TEAM	Treatment of Early Age Mania
TF-CBT	trauma-focused cognitive behavioural therapy
TFT	thyroid function test
THC/CBD	tetrahydrocannabinol/cannabidiol
TIA	transient ischaemic attack
TMS	transcranial magnetic stimulation

TORDIA	Treatment of Resistant Depression in Adolescence
TPR	temperature, pulse, respiration
TRS	treatment-resistant schizophrenia
TS	Tourette syndrome
U&Es	urea and electrolytes
UGIB	upper gastrointestinal bleeding
UGT	UDP-glucuronosyl transferase
VaD	vascular dementia
VNS	vagal nerve stimulation
VTE	venous thromboembolism
WBC	white blood cell
WCC	white cell count
WHO	World Health Organization
XL	extended release
YMRS	Young Mania Rating Scale
ZA	zuclopenthixol acetate

Part 1

Drug treatment of major psychiatric conditions

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 and 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 symptoms (EPS) 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 EPS and its failure in animal-based antipsychotic screening tests. Its re-marketing in 1990 signalled the beginning of a series of new medications, all of which were introduced with claims (of varying degrees of accuracy) of 'atypicality'. Of these medications, perhaps only clozapine and, possibly, quetiapine are completely atypical, seemingly having a very low

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

liability for EPS. Others show dose-related effects, although, unlike with typical drugs, therapeutic activity can usually be achieved without EPS. 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), which is effective but does not cause EPS (e.g. compare haloperidol with olanzapine).

The typical/atypical dichotomy does not lend itself well to classification of antipsychotics in the middle ground of EPS liability. Thioridazine was widely described as atypical in the 1980s but is a 'conventional' phenothiazine. Sulpiride was marketed as atypical but is often classified as typical. Risperidone, at its maximum dose of 16mg/day (10mg in the USA), 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) 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 around 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 atypically, whatever atypicality 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 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

The 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 of 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, but 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

Following 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 is somewhat offset by a higher propensity to cause metabolic side 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, initial summary data suggested 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 side 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] 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.[16]

Clozapine is clearly the drug of choice in refractory schizophrenia[17] although, bizarrely, this is not a universal finding,[18] probably because of the nature and quality of many active-comparator trials.[19,20]

Both FGAs and SGAs are associated with a number of adverse effects. These include weight gain, dyslipidaemia, increases in plasma glucose/diabetes,[21,22] hyperprolactinaemia, hip fracture,[23] sexual dysfunction, EPS including neuroleptic malignant syndrome,[24] anticholinergic effects, venous thromboembolism (VTE),[25] sedation and postural hypotension. The exact profile is drug-specific (see individual sections on

specific adverse effects), although comparative data are not robust[26] (see largescale meta-analyses[13,27] for rankings of some adverse effect risks).

Adverse effects are a common reason for treatment discontinuation,[28] particularly when efficacy is poor.[13] Patients do not always spontaneously report side effects however,[29] and psychiatrists' views of the prevalence and importance of adverse effects differ markedly from patient experience.[30] Systematic enquiry, along 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)[31] can be a useful first step in this process. The clinician-completed Antipsychotic Non-Neurological Side-Effects Rating Scale (ANNSERS) facilitates a more detailed and comprehensive assessment.[32]

Non-adherence to antipsychotic treatment is common, and here the guaranteed medication delivery associated with depot/long-acting injectable antipsychotic preparations is unequivocally advantageous. In comparison with oral antipsychotics, there is strong evidence that depots are associated with a reduced risk of relapse and rehospitalisation.[33–35] The introduction of SGA long-acting injections 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 a month, with flupentixol, which has a licensed dose in the UK of 50mg every four weeks to 400mg a week). The optimal dose of flupentixol is around 40mg every 2 weeks:[27] 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,[36–38] and its use in these circumstances is recommended by NICE.[3] The biological basis for the superior efficacy of clozapine is uncertain.[39] Olanzapine should probably be one of the two drugs used before clozapine.[10,40] 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.[41] This 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. A review of the current nomenclature for psychotropic agents and an introduction to the Neuroscience-based Nomenclature. *Eur Neuropsychopharmacol* 2015; 25:2318–2325.
2. National Institute for Clinical Excellence. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. Clinical Guidance [CG76]. 2009 (last checked March 2019); https://www.nice.org.uk/Guidance/CG76.
3. National Institute for Health and Care Excellence. Psychosis and schizophrenia in adults: prevention and management. Clinical Guidance [CG178]. 2014 (last checked March 2019); 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 Neuro Psychopharmacol* 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* 2017; **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. *Arch Gen 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* 2004; **171**:121–132.
16. 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.
17. 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.
18. Samara MT, et al. Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: a network meta-analysis. *JAMA Psychiatry* 2016; **73**:199–210.
19. Taylor DM. Clozapine for treatment-resistant schizophrenia: still the gold standard? *CNS Drugs* 2017; **31**:177–180.
20. Kane JM, et al. The role of clozapine in treatment-resistant schizophrenia. *JAMA Psychiatry* 2016; **73**:187–188.
21. Manu P, et al. Prediabetes in patients treated with antipsychotic drugs. *J Clin Psychiatry* 2012; **73**:460–466.
22. 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.
23. Sorensen HJ, et al. Schizophrenia, antipsychotics and risk of hip fracture: a population-based analysis. *Eur Neuro Psychopharmacol* 2013; **23**:872–878.
24. Trollor JN, et al. Comparison of neuroleptic malignant syndrome induced by first- and second-generation antipsychotics. *Br J Psychiatry* 2012; **201**:52–56.
25. Masopust J, et al. Risk of venous thromboembolism during treatment with antipsychotic agents. *Psychiatry Clin Neurosci* 2012; **66**:541–552.
26. 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.
27. Bailey L, et al. Estimating the optimal dose of flupentixol decanoate in the maintenance treatment of schizophrenia-a systematic review of the literature. *Psychopharmacology* 2019; **236**:3081–3092.
28. Falkai P. Limitations of current therapies: why do patients switch therapies? *Eur Neuropsychopharmacol* 2008; **18 Suppl 3**:S135–S139.
29. 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.
30. 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.
31. Waddell L, et al. A new self-rating scale for detecting atypical or second-generation antipsychotic side effects. *J Psychopharmacology* 2008; **22**:238–243.
32. 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.
33. 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.
34. 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.
35. Leucht S, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet* 2012; **379**:2063–2071.
36. Kane J, et al. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988; **45**:789–796.
37. 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.
38. 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.
39. Stone JM, et al. Review: the biological basis of antipsychotic response in schizophrenia. *J Psychopharmacology* 2010; **24**:953–964.
40. 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.
41. 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.

General principles of prescribing

- The **lowest possible** dose should be used. For each patient, the dose should be titrated to the lowest known to be effective (see the section on minimum effective doses); dose increases should then take place only after one or two weeks of assessment during which the patient is clearly showing poor or no response. (There is gathering evidence that lack of response at 2 weeks is a potent predictor of later poor outcome, unless dose or drug is changed.)
- With regular dosing of **long-acting injections**, plasma levels rise for at least 6–12 weeks after initiation, even without a change in dose (see the section on depot pharmacokinetics in this chapter). Dose increases during this time are therefore difficult to evaluate. The preferred method is to establish efficacy and tolerability of oral medication at a particular dose and then give the equivalent dose of that drug in LAI form. Where this is not possible, the target dose of LAI for an individual should be that established to be optimal in clinical trials (although such data are not always available for older LAIs).
- For the large majority of patients, the use of a **single antipsychotic** (with or without additional mood stabiliser or sedatives) is recommended. Apart from exceptional circumstances (e.g. clozapine augmentation), antipsychotic polypharmacy should generally be avoided because of the increased adverse effect burden and risks associated with QT prolongation and sudden cardiac death (see the section on combined antipsychotics in this chapter).
- **Combinations** of antipsychotics should only be used where response to a single antipsychotic (including clozapine) has been clearly demonstrated to be inadequate. In such cases, the effect of the combination against target symptoms and adverse effects should be carefully evaluated and documented. Where there is no clear benefit, treatment should revert to single antipsychotic therapy.
- In general, **antipsychotics should not be used as 'when necessary' sedatives**. Time-limited prescriptions of benzodiazepines or general sedatives (e.g. promethazine) are recommended (see the section on rapid tranquillisation in this chapter).
- Responses to antipsychotic drug treatment should be **assessed using recognised rating scales** and outcomes documented in patients' records.
- Those receiving antipsychotics should undergo close monitoring of physical health (including blood pressure, pulse, ECG, plasma glucose and plasma lipids) (see appropriate sections in this chapter).
- When withdrawing antipsychotics, reduce the dose slowly in a hyperbolic regimen which minimises the risks of withdrawal symptoms and rebound psychosis.

[*Note*: This section is not referenced. Please see relevant individual sections in this chapter for detailed and referenced guidance.]

Minimum effective doses

Table 1.1 suggests the minimum dose of antipsychotic likely to be effective in first- or multi-episode schizophrenia. Most patients will respond to the dose suggested, although others may require higher doses. Given the variation in individual response, all doses should be considered approximate. Primary references are provided where available, but consensus opinion has also been used. Only oral treatment with commonly used drugs is covered.

Table 1.1 Minimum effective dose/day – antipsychotics

Drug	First episode	Multi-episode
FGAs		
Chlorpromazine[1]	200mg*	300mg
Haloperidol[2–7]	2mg	4mg
Sulpiride[8]	400mg*	800mg
Trifluoperazine[9,10]	10mg*	15mg
SGAs		
Amisulpride[11–16]	300mg*	400mg*
Aripiprazole[7,17–22]	10mg	10mg
Asenapine[7,22,23]	10mg*	10mg
Blonanserin[24]	Not known	8mg
Brexpiprazole[25–27]	2mg*	4mg
Cariprazine[28,29]	1.5mg*	1.5mg
Iloperidone[7,21,22,30]	4mg*	8mg
Lumateperone[31]	Not known	42mg*
Lurasidone[7,32]	40mg HCl/37mg base*	40mg HCl/37mg base
Olanzapine[4,7,33–35]	5mg	7.5mg
Paliperidone[22]	3mg*	3mg
Pimavanserin[36–38]	Not known	34mg**
Quetiapine[39–44]	150mg* (but higher doses often used[45])	300mg
Risperidone[3,7,46–49]	2mg	4mg
Ziprasidone[7,21,50–52]	40mg*	80mg

*Estimate – too few data available
**FDA-approved for Parkinson's disease psychosis; dose in schizophrenia not known