The Maudsley®

Prescribing Guidelines in Psychiatry

14TH EDITION

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

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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

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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

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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*.

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Andrea Danese
Andrew Wilcock
Annabel Price
Anne Connolly
Bruce Clark
Claire Wilson
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Daniel Harwood
David Mirfin
Deborah Robson
Delia Bishara
Derek Tracy
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Ian Osborne
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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.

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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

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Licensed maximum doses

The following table lists the licensed maximum doses of antipsychotics according to the EMA labelling as of February 2021.

Drug	Maximum dose
FGAs – oral	
Chlorpromazine	1000mg/day
Flupentixol	18mg/day
Haloperidol	20mg/day
Levomepromazine	1200mg/day
Pericyazine	300mg/day
Perphenazine	24mg/day (64mg/day hospitalised patients)
Pimozide	20mg/day
Sulpiride	2400mg/day
Trifluoperazine	20mg/day
Zuclopenthixol	150mg/day
SGAs – oral	
Amisulpride	1200mg/day
Aripiprazole	30mg/day
Asenapine	20mg/day (sublingual)
Cariprazine	6mg/day
Clozapine	900mg/day
Lurasidone	160mg (HCl)/148mg (base)/day
Olanzapine	20mg/day
Paliperidone	12mg/day
Quetiapine	750mg/day schizophrenia (800mg/day for MR preparation) 800mg/day bipolar disorder
Risperidone	16mg/day
Sertindole	24mg/day
Long-acting injections	
Aripiprazole depot	400mg/month
Flupentixol depot	400mg/week
Fluphenazine depot	100mg every 14–35 days
Haloperidol depot	300mg every 4 weeks
Paliperidone depot 1-monthly	150mg/month

Drug	Maximum dose
Paliperidone depot 3-monthly	525mg every 3 months
Pipotiazine depot	200mg every 4 weeks
Risperidone (Janssen)	50mg every 2 weeks
Zuclopenthixol depot	600mg/week

The following table lists the licensed maximum doses of antipsychotics available outside the EU, according to FDA labelling (as of February 2021)

Drug	Maximum dose
SGAs – oral	
Blonanserin*	24mg/day oral[1] (80mg/day patch[2])
Brexpiprazole	4mg/day
Iloperidone	24mg/day
Lumateperone	42mg/day
Molindone	225mg/day
Pimavanserin	34mg/day
RBP-7000 (risperidone 1-monthly)	120mg/month
Ziprasidone	160mg/day

*Available only in China, Japan and South Korea at the time of writing.

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Equivalent doses

Knowledge of equivalent dosages is useful when switching between FGAs. Estimates of 'neuroleptic' or 'chlorpromazine' equivalence, in milligrams a day, between these medications are based on clinical experience, expert panel opinion (using various methods) and any dopamine binding studies available.

Table 1.2 provides approximate equivalent doses for FGAs.[1–4] The values given should be seen as a rough guide when switching from one FGA to another and are no substitute for clinical titration of the new medication dose against adverse effects and response.

Equivalent doses of SGAs may be less clinically relevant as these medications tend to have better defined, evidence-based licensed dose ranges. There are several different ways of calculating equivalence based on, for example, defined daily dose,[5] minimum effective dose[6,7] and average dose.[8] These methods give different estimates of equivalence. A very rough guide to equivalent SGA daily dosages is given in the Table 1.3.[3,4,7–9] There is considerable disagreement about exact equivalencies, even amongst the references cited here. Clozapine is not included because this has a distinct initial titration schedule and a high dose-plasma level variability and because it probably has a different mechanism of action.

Comparing potencies of FGAs with SGAs introduces yet more uncertainty with respect to dose equivalence. Very approximately, 100mg chlorpromazine is equivalent to 1.5mg risperidone.[3]

Table 1.2 Equivalent doses of first generation antipsychotics

Drug	Equivalent dose (consensus)	Range of values in literature
Chlorpromazine	100mg/day	Reference
Flupentixol	3mg/day	2–3mg/day
Flupentixol depot	10mg/week	10–20mg/week
Fluphenazine	2mg/day	1–5mg/day
Fluphenazine depot	5mg/week	1–12.5mg/week
Haloperidol	2mg/day	1.5–5mg/day
Haloperidol depot	15mg/week	5–25mg/week
Pericyazine	10mg/day	10mg/day
Perphenazine	10mg/day	5–10mg/day
Pimozide	2mg/day	1.33–2mg/day
Pipotiazine depot	10mg/week	10–12.5mg/week
Sulpiride	200mg/day	133–300mg/day
Trifluoperazine	5mg/day	2.5–5mg/day
Zuclopenthixol	25mg/day	25–60mg/day
Zuclopenthixol depot	100mg/week	40–100mg/week

Table 1.3 Second-generation antipsychotics – approximate equivalent doses[3–10]

Drug	Approximate equivalent dose
Amisulpride	400mg
Aripiprazole	15mg
Asenapine	10mg
Blonanserin	~
Brexpiprazole	2mg
Cariprazine	1.5mg
Clotiapine	100mg
Iloperidone	12mg
Lumateperone	~
Lurasidone	80mg (74mg base)
Melperone	300mg
Molindone	50mg
Olanzapine	10mg
Paliperidone LAI	100mg/month
Pimavanserin	~
Quetiapine	400mg
Risperidone oral	4mg
Risperidone LAI	50mg/2 weeks
Risperidone RBP-7000	120mg/month
Ziprasidone	80mg

~Unknown equivalence at time of writing.

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High-dose antipsychotics: prescribing and monitoring

'High dose' antipsychotic medication can result from the prescription of either a single antipsychotic medication at a dose above the recommended maximum or two or more antipsychotic medications concurrently that, when expressed as a percentage of their respective maximum recommended doses and added together, result in a cumulative dose of more than 100%.[1] In clinical practice, antipsychotic polypharmacy and PRN antipsychotic medication are strongly associated with high-dose prescribing.[2,3]

Efficacy

There is no firm evidence that high doses of antipsychotic medication are any more effective than standard doses for schizophrenia. This holds true for the use of antipsychotic medication for rapid tranquillisation, relapse prevention, persistent aggression and the management of acute psychotic episodes.[1] Despite this, in the UK, approximately a quarter to a third of hospitalised patients on antipsychotic medication have been observed to be on a high dose,[2] while the national audit of schizophrenia in 2013, reporting on prescribing practice for over 5,000 predominantly community-based patients, found that, overall, 10% were prescribed a high dose of antipsychotic medication.[4]

Examination of the dose–response effects of a variety of antipsychotic medications has not found any evidence of greater efficacy for doses above accepted licensed ranges.[5,6] Efficacy appears to be optimal at relatively low doses: 4mg/day risperidone;[7] 300mg/day quetiapine,[8] olanzapine 10mg,[9,10] etc. Similarly, treatment with LAI risperidone at a dose of 100mg 2-weekly offers no benefits over 50mg 2-weekly,[11] and 320mg/day ziprasidone[12] is no better than 160mg/day. All currently available antipsychotic medications (with the possible exception of clozapine) exert their antipsychotic effect primarily through antagonism (or partial agonism) at post-synaptic dopamine receptors. There is increasing evidence that in some patients with schizophrenia, refractory symptoms do not seem to be driven through dysfunction of dopamine pathways,[13–16] and so increasing dopamine blockade in such patients is of uncertain value. Just as importantly, the law of mass action dictates that dose increases bring about successively smaller increases in dopamine occupancy once the threshold for efficacy has been reached.[17]

Dold et al.[18] conducted a meta-analysis of RCTs that compared continuation of standard-dose antipsychotic medication with dose escalation in patients whose schizophrenia had proved to be unresponsive to a prospective trial of standard-dose pharmacotherapy with the same antipsychotic medication. In this context, there was no evidence of any benefit associated with the increased dosage. There are a small number of RCTs that have examined the efficacy of high versus standard dosage in patients with a diagnosis of treatment-resistant schizophrenia (TRS).[1] Some demonstrated benefit,[19] but the majority of these studies are old, the number of patients randomised is small and study design is poor by current standards. Some studies used daily doses equivalent to more than 10g chlorpromazine.

In a study of patients with first-episode schizophrenia, increasing the dose of olanzapine up to 30mg/day and the dose of risperidone up to 10mg/day in non-responders to standard doses yielded only a 4% absolute increase in overall response rate; switching to an alternative antipsychotic, including clozapine, was considerably more successful.[20] One small (n = 12) open study of high-dose quetiapine (up to 1400mg/day) found modest benefits in a third of subjects,[21] but other, larger studies of quetiapine have shown no benefit for higher doses.[8,22,23] A further RCT of high-dose olanzapine (up to 45mg/day) versus clozapine for treatment-resistant schizophrenia found similar efficacy for the two treatments, but concluded that, given the small sample size, it would be premature to conclude that they were equivalent.[24] A systematic review of relevant studies comparing olanzapine at above standard dosage with clozapine for TRS concluded that while olanzapine, particularly in higher dosage, might be considered as an alternative to clozapine in TRS, clozapine still had the most robust evidence for efficacy.[25]

The most recent systematic analysis of dose response[26] largely confirmed the observation of a flat or horizontal dose–response curve above a certain dose for all antipsychotics, with the possible exceptions of olanzapine and lurasidone (with these two drugs, there is evidence that doses at the upper end of the licensed range are somewhat more effective than lower doses[10,27]). This systematic review also suggested that doses above which no additional benefit was likely were somewhat higher than those stated above, e.g. risperidone 6.3mg/day; quetiapine 482mg/day. Importantly, however, there was no evidence to support the use of doses of any drug above its licensed does range.

Adverse effects

The majority of side effects associated with antipsychotic treatment are dose-related. These include EPS, sedation, postural hypotension, anticholinergic effects, QTc prolongation and coronary heart disease mortality.[28–31] High-dose antipsychotic treatment is clearly associated with a greater side-effect burden.[12,23,28,32,33] There is some evidence that antipsychotic dose reduction from very high (mean 2253mg chlorpromazine equivalents per day) to high (mean 1315mg chlorpromazine equivalents per day) dose leads to improvements in cognition and negative symptoms.[34]

Recommendations

- The use of high-dose antipsychotic medication should be an exceptional clinical practice and only ever employed when adequate trials of standard treatments, including clozapine, have failed.
- If high-dose antipsychotic medication is prescribed, it should be standard practice to review and document the target symptoms, therapeutic response and side effects, ideally using validated rating scales, so that there is ongoing consideration of the risk-benefit ratio for the patient. Close physical monitoring (including ECG) is essential.

Prescribing high-dose antipsychotic medication

Before using high doses, ensure that:

- Sufficient time has been allowed for response (see section on time to response).
- At least two different antipsychotic medications have been tried sequentially (including, if possible, olanzapine).
- Clozapine has failed or not been tolerated due to agranulocytosis or other serious adverse effect. Most other side-effects can be managed. A small proportion of patients may also decline to take a clozapine regimen.
- Medication adherence is not in doubt (use of blood tests, liquids/dispersible tablets, depot/LAI antipsychotic preparations, etc).
- Adjunctive medications such as antidepressants or mood stabilisers are not indicated.
- Psychological approaches have failed or are not appropriate.

The decision to use high doses should:

- Be made by a senior psychiatrist
- Involve the multidisciplinary team
- Be done, if possible, with a patient's informed consent

Process

- Rule out contraindications (ECG abnormalities, hepatic impairment)
- Consider and minimise any risks posed by concomitant medication (e.g. potential to cause QTc prolongation, electrolyte disturbance or pharmacokinetic interactions via CYP inhibition)
- Document the decision to prescribe high dosage in the clinical notes along with a description of target symptoms. The use of an appropriate rating scale is advised
- Adequate time for response should be allowed after each dosage increment before a further increase is made

Monitoring

- Physical monitoring should be carried out as outlined in the section on monitoring
- All patients on high doses should have regular ECGs (base-line, when steady-state serum levels have been reached after each dosage increment, and then every 6 to 12 months) Additional biochemical/ECG monitoring is advised if drugs that are known to cause electrolyte disturbances or QTc prolongation are subsequently co-prescribed
- Target symptoms should be assessed after 6 weeks and 3 months. If insufficient improvement in these symptoms has occurred, the dose should be decreased to the normal range

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Combined antipsychotics (antipsychotic polypharmacy)

In psychiatric practice, prescriptions for combined antipsychotic medications are common[1–3] and often long term.[4] The medications combined are likely to include LAI antipsychotic preparations,[5,6] quetiapine[7] and FGAs,[8] the last of these perhaps reflecting the frequent use of haloperidol and chlorpromazine as PRN medications.

Poor response to antipsychotic monotherapy

National clinical audits conducted in the UK as part of a Prescribing Observatory for Mental Health (POMH-UK) quality improvement programme[9] found that the most common reasons recorded for prescribing regular, combined antipsychotic medications were a poor response to antipsychotic monotherapy and a period of crossover while switching from one antipsychotic to another. The use of combined antipsychotic medications has been found to be associated with younger patient age, male gender, and increased illness severity, complexity and chronicity, as well as poorer functioning, inpatient status and a diagnosis of schizophrenia.[2,7,10–12] These associations largely reinforce the notion that antipsychotic polypharmacy is used where schizophrenia has proved to be refractory to trials of antipsychotic monotherapy.[10,13–15]

Nonetheless, there is a lack of robust evidence that the efficacy of combined antipsychotic medications is superior to treatment with a single antipsychotic.[16] A meta-analysis of 16 RCTs in schizophrenia, comparing augmentation with a second antipsychotic with continued antipsychotic monotherapy, found that combining antipsychotic medications lacked double-blind/high-quality evidence for overall efficacy.[17] Furthermore, in patients with schizophrenia, the effects of a change back from antipsychotic polypharmacy to monotherapy, even when carefully conducted, are uncertain. While the findings of two randomised studies suggested that the majority of patients may be successfully switched from antipsychotic polypharmacy to monotherapy without loss of symptom control,[18,19] another reported greater increases in symptoms after six months in those participants who had switched to antipsychotic monotherapy,[20] although the expectation is that such exacerbations can be successfully managed.[18]

Long-term antipsychotic treatment

A non-interventional, population-based study in Hungary, sought to compare the effectiveness of antipsychotic monotherapy with the use of combined antipsychotic medications over a one-year observation period. The investigators concluded that while the results provided evidence for the superiority of monotherapy over polypharmacy for SGAs in terms of all-cause treatment discontinuation in schizophrenia, polypharmacy was associated with a lower likelihood of mortality and psychiatric hospitalisations.[21] Similarly, a 20-year, observational study in Finland reported on the risk of rehospitalisation in a cohort of 62,250 hospital-treated patients with schizophrenia. To minimise selection bias, the investigators used within-individual analyses, with each patient used as their own control. The main finding was that antipsychotic combinations, particularly those including clozapine and LAI antipsychotic medications, were associated with a slightly lower risk of psychiatric rehospitalisation than monotherapy.[22] Although

the interpretation of such real-world findings is hindered by the issue of confounding by indication,[23] there are perhaps several plausible explanations. It may be that combining antipsychotic medications with different receptor profiles can be more effective and lead to better therapeutic efficacy and/or a lower side-effect burden and therefore better outcomes. It may also be that co-prescribing two antipsychotic medications improves medication adherence in that it increases the likelihood that a patient may use at least one of them.[22] A more complicated and speculative explanation relates to the finding that, in clinical practice, clozapine and LAI antipsychotic preparations appear to be the most effective monotherapies for relapse prevention in schizophrenia.[24] Thus, adding a second antipsychotic medication to clozapine or an LAI antipsychotic medication in an attempt to mitigate metabolic side effects (e.g. by adding aripiprazole) or manage symptoms of agitation, anxiety or sleep disturbance (e.g. by adding olanzapine or quetiapine) might enhance a patient's engagement in their treatment and improve adherence to the effective antipsychotic treatment that has been augmented.

Adverse effects

Evidence for possible harm with combined antipsychotic medications is perhaps more convincing. Clinically significant side effects have been associated with combined antipsychotic medications, which may partly reflect that such a regimen is commonly a high-dose prescription.[8,25] There are reports of an increased prevalence and severity of EPS,[26,27] increased metabolic side effects and diabetes,[20,28,29] sexual dysfunction,[30] an increased risk of hip fracture,[31] paralytic ileus,[32] grand mal seizures,[33] prolonged QTc[34] and arrhythmias.[13] Switching from antipsychotic polypharmacy to monotherapy has been shown to lead to worthwhile improvements in cognitive functioning.[19]

The evidence relating to an increased mortality with a continuing antipsychotic polypharmacy regimen is inconsistent. Two large case–control studies and a database study[35–37] found no increased mortality in patients with schizophrenia receiving antipsychotic polypharmacy, compared with antipsychotic monotherapy. However, a 10-year prospective study of a cohort of 88 patients with schizophrenia reported that receiving more than one antipsychotic medication concurrently was associated with substantially increased mortality.[17,38] These investigators explored the possibility that the use of combined antipsychotic medications might be a proxy for greater severity/increased refractoriness of psychiatric illness but found no association between mortality and any measured index of illness severity, although these measures focussed on negative symptoms and cognitive deficits. Furthermore, analysis of data from a large anonymised mental healthcare database (2007–2014) of 10,945 adult patients with serious mental illness who had been prescribed a single antipsychotic or polypharmacy for six months or more, revealed a weak association between regular, long-term antipsychotic polypharmacy and all-cause mortality and natural causes of death.[39] However, the authors concluded that the evidence for the association was limited, even after controlling for the effect of dose. Another study, involving the follow-up of 99 patients with schizophrenia over a 25-year period, found that those prescribed three antipsychotics simultaneously were twice as likely to die as those who had been prescribed only one.[40] These authors also considered the possibility of indication bias influencing the findings, speculating that combined antipsychotic medication might be more likely to be prescribed for the most severe schizophrenia.

Given the association between combined antipsychotic medication and a greater side-effect burden,[15,41] it follows that it should be standard practice to document in the clinical records the rationale for prescribing combined antipsychotics in individual cases, along with a clear account of the benefits and side effects of an individual trial of the strategy. Medico-legally, this would seem to be prudent although in practice it is rarely done.[42]

The use of combined antipsychotic medications in clinical practice

There are myriad possible antipsychotic medication combinations but very limited data on their relative risk–benefit profiles in relation to overall therapeutic response or target symptom clusters. The clinical disadvantages of antipsychotic polypharmacy include an increased side-effect burden, higher total dosage, increased risk of drug–drug interactions, poorer medication adherence related to the complexity of the treatment, and difficulties in the attribution of any response to one or more of the individual antipsychotic medications prescribed, leading to difficulty in determining the implications for an optimal longer-term regimen.[6]

Despite the limited supportive evidence base, the use of antipsychotic polypharmacy is an established custom and practice in many countries.[43–45] Furthermore, the general consensus across treatment guidelines that the use of combined antipsychotic medication for the treatment of refractory psychotic illness should be considered only after other, evidence-based, pharmacological treatments such as clozapine have been exhausted, is not consistently followed in clinical practice.[6,12,13,46–48] However, it should be noted that a trial of clozapine augmentation with a second antipsychotic medication to enhance efficacy is a potentially supportable practice[49–53] (see the section on clozapine augmentation in this chapter). Other antipsychotic polypharmacy strategies with potentially valid rationales are the addition of aripiprazole to reduce body weight in patients receiving clozapine[54,55] and to normalise prolactin levels in those on haloperidol[56] and risperidone LAI[57] (although not amisulpride[58]). Polypharmacy with aripiprazole in such circumstances may thus represent worthwhile, evidence-based practice, albeit in the absence of regulatory trials demonstrating safety. In many cases, however, using aripiprazole alone might be a more logical choice.

Conclusion

Some of the findings reported above might be considered to challenge the prevailing consensus that prescribing more than one antipsychotic medication is unlikely to improve efficacy and may increase medical morbidity.[59,60] Nevertheless, on the evidence currently available relating to efficacy and the potential for serious adverse effects, the routine use of combined, non-clozapine, antipsychotic medications may be best avoided.

Summary

- There is a lack of robust evidence supporting the efficacy of combined, non-clozapine, antipsychotic medications
- There is substantial evidence supporting the potential for harm and so the use of combined antipsychotic medications, which is commonly a high-dose prescription, should generally be avoided.
- Combined antipsychotic medications are commonly prescribed and this practice seems to be relatively resistant to change
- As a minimum requirement, all patients who are prescribed combined antipsychotic medications should be systematically monitored for side effects (including an ECG) and any beneficial effect on the symptoms of psychotic illness carefully documented.
- Some antipsychotic polypharmacy strategies (e.g. combinations with aripiprazole) show benefits for tolerability but not efficacy.

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Antipsychotic prophylaxis

First episode of psychosis

Antipsychotics provide effective protection against relapse, at least in the short to medium term[1] and the introduction of antipsychotics in the 1950s seems to have improved outcomes overall.[2] A meta-analysis of placebo-controlled trials found that 26% of first-episode patients randomised to receive maintenance antipsychotic relapsed after 6–12 months compared with 61% randomised to receive placebo.[3] Although the current consensus is that antipsychotics should be prescribed for 1–2 years after a first episode of schizophrenia,[4,5] one study[6] found that withdrawing antipsychotic treatment in line with this consensus led to a relapse rate of almost 80% after one year medication-free and 98% after 2 years. A 2019 Swedish population study revealed that the longer the treatment with antipsychotics, the lower the risk of hospitalisation (e.g. those with 5 years' treatment had half the hospitalisation rate of those treated for less than 6 months).[7]

Other studies in first-episode schizophrenia confirmed that only a small minority of patients who discontinue remain well 1–2 years later[8–11] (e.g. a small study found 94% of first-episode patients relapsed within 2 years of stopping risperidone long-acting injection, 97% at three years[12]). A 2018 meta-analysis of 8 RCTs was rather more optimistic and found relapse rates averaged 35% (treated) and 61% (discontinued) at 18–24 months.[13]

A 5-year follow-up of a 2-year RCT during which patients received either maintenance antipsychotic treatment or had their antipsychotic dose reduced or discontinued completely found that while there was a clear advantage for maintenance treatment with respect to reducing short-term relapse this advantage was lost in the medium-term. Furthermore, the dose-reduction/discontinuation group were receiving lower doses of antipsychotic drugs at follow-up and had better functional outcomes.[14] There are numerous interpretations of these outcomes, but the most that can be concluded is that dose reduction is a possible option in first-episode psychosis. The study has been heavily criticised[15] and here are certainly other studies showing disastrous outcomes from antipsychotic discontinuation,[16] albeit over shorter periods with fewer subjects. Nonetheless, some patients with first-episode psychosis will not need long-term antipsychotics to stay well – figures as high as 18–30% have been put forward.[17]

There are no reliable patient factors linked to outcome following discontinuation of antipsychotics in first-episode patients (other than cannabis use[18]), and there remains more evidence in favour of continuing antipsychotics than for stopping them.[19] There are indications that very prolonged discontinuation regimens using hyperbolic tapering (see the section of stopping antipsychotics) may offer the best chance of successfully withdrawing from antipsychotic treatment.[20,21]

It should be noted that definitions of relapse usually focus on the severity of positive symptoms, and largely ignore cognitive and negative symptoms: positive symptoms are more likely to lead to hospitalisation while cognitive and negative symptoms (which respond less well, and in some circumstances may even be exacerbated by antipsychotic treatment) have a greater overall impact on quality of life.

With respect to antipsychotic choice, in the context of an RCT, clozapine did not offer any advantage over chlorpromazine in the medium term in first-episode patients with non-refractory illness.[22] But in a large naturalistic study of patients with a first admission for schizophrenia, clozapine and olanzapine fared better with respect to

preventing readmission than other oral antipsychotics.[23] In this same study, the use of a long-acting antipsychotic injection seemed to offer advantages over oral antipsychotics despite confounding by indication (depots will have been prescribed to those considered to be poor adherers, oral to those perceived to have good adherence[23]). Later studies show a huge advantage for long-acting risperidone over oral risperidone in first-episode patients[24] and a smaller but substantial benefit for paliperidone LAI over oral antipsychotics in 'recently diagnosed schizophrenia'.[25] In the latest study, amisulpride was shown to give good outcomes and staying on amisulpride after not initially reaching remission was as successful as switching to olanzapine.[26]

In practice, a firm diagnosis of schizophrenia is rarely made after a first episode, and the majority of prescribers and/or patients will have at least attempted to stop antipsychotic treatment within one year.[27] Ideally, patients should have their dose reduced very gradually, and all relevant family members and healthcare staff should be aware of the discontinuation (such a situation is most likely to be achieved by using long-acting injection). It is vital that patients, carers and key-workers are aware of the early signs of relapse and how to access help. Antipsychotics should not be considered the only intervention. Evidence-based psychosocial and psychological interventions are clearly also important.[28]

Multi-episode schizophrenia

The majority of those who have one episode of schizophrenia will go on to have further episodes. Patients with residual symptoms, a greater side effect burden and a less positive attitude to treatment are at greater risk of relapse.[29] With each subsequent episode, the baseline level of functioning deteriorates,[30] and the majority of this decline is seen in the first decade of illness. Suicide risk (10%) is also concentrated in the first decade of illness. Antipsychotic drugs, when taken regularly, protect against relapse in the short, medium and (less certainty) long term.[3,31] Those who receive targeted antipsychotics (i.e. only when symptoms re-emerge) seem to have a worse outcome than those who receive prophylactic antipsychotics,[32,33] and the risk of TD may also be higher. Similarly, low-dose antipsychotics are less effective than standard doses.[34]

Following table summarises the known benefits and harms associated with maintenance antipsychotic treatment as reported in a meta-analysis by Leucht et al. (2012).[3]

Benefits				**Harms**			
Outcome	**Antipsychotic**	**Placebo**	**NNT**	**Adverse effect**	**Antipsychotic**	**Placebo**	**NNH***
Relapse at 7–12 months	27%	64%	3	Movement disorder	16%	9%	17
Re-admission	10%	26%	5	Anticholinergic effects	24%	16%	11
Improvement in mental state	30%	12%	4	Sedation	13%	9%	20
Violent/aggressive behaviour	2%	12%	11	Weight gain	10%	6%	20

NNT = number needed to treat for one patient to benefit; NNH = number treated for one patient to be harmed.
*Likely to be a considerable underestimate as adverse effects are rarely systematically assessed in clinical trials.[35]

Depot preparations may have an advantage over oral in maintenance treatment, most likely because of guaranteed medication delivery (or at least guaranteed awareness of medication delivery). Meta-analyses of clinical trials have shown that the relative and absolute risks of relapse with depot maintenance treatment were 30% and 10% lower, respectively, than with oral treatment.[3,36] Long-acting preparations of antipsychotics may thus be preferred by both prescribers and patients.

Summary

- Relapse rates in patients discontinuing antipsychotics are extremely high.
- Antipsychotics significantly reduce relapse, re-admission and violence/aggression.
- Long-acting depot formulations provide the best protection against relapse.

A large meta-analysis concluded that the risk of relapse with newer antipsychotics is similar to that associated with older drugs.[3] (Note that lack of relapse is not the same as good functioning.[37]) The proportion of multi-episode patients who achieve remission is small and may differ between antipsychotic drugs. The CATIE study reported that only 12% of patients treated with olanzapine achieved remission for at least 6 months, compared with 8% treated with quetiapine and 6% with risperidone.[38] The advantage seen here for olanzapine is consistent with that seen in an acute efficacy network meta-analysis.[39]

Adherence to antipsychotic treatment

Amongst people with schizophrenia, non-adherence with antipsychotic treatment is high. Only 10 days after discharge from hospital up to 25% are partially or non-adherent, rising to 50% at 1 year and 75% at 2 years.[40] Not only does non-adherence increase the risk of relapse, it may also increase the severity of relapse and the duration of hospitalisation.[40] The risk of suicide attempts also increases four-fold[40].

Dose for prophylaxis

Many patients probably receive higher doses than necessary (particularly of the older drugs) when acutely psychotic.[41,42] In the longer term a balance needs to be made between effectiveness and adverse effects. Lower doses of the older drugs (8mg haloperidol/day or equivalent) are, when compared with higher doses, associated with less severe side effects,[43] better subjective state and better community adjustment.[44] Very low doses increase the risk of psychotic relapse.[41,45,46] There are no data to support the use of lower than standard doses of the newer drugs as prophylaxis. Doses that are acutely effective should generally be continued as prophylaxis,[47,48] although an exception to this is prophylaxis after a first episode where very careful dose reduction is probably supportable. There is some recent support for dose reduction in multi-episode schizophrenia,[49] and there are a number of trials in progress at the time of writing.[50–52]

How and when to stop[53]

The decision to stop antipsychotic drugs requires a thorough risk–benefit analysis for each patient. Withdrawal of antipsychotic drugs after long-term treatment should be gradual and closely monitored. The relapse rate in the first 6 months after abrupt withdrawal is double that seen after gradual withdrawal (defined as slow taper down over at least 3 weeks for oral antipsychotics or abrupt withdrawal of depot preparations).[54] One analysis of incidence of relapse after switch to placebo found time to relapse to be very much longer for 3-monthly paliperidone than for 1-monthly and oral.[55] Overall percentage relapse was also reduced. Abrupt withdrawal of oral treatment may also lead to discontinuation symptoms (e.g. headache, nausea, insomnia) in some patients.[56]

The following factors should be considered:[53]

- Is the patient symptom-free, and if so, for how long? Long-standing, non-distressing symptoms which have not previously been responsive to medication may be excluded.
- What is the severity of adverse-effects (EPS, TD, sedation, obesity, etc.)?
- What was the previous pattern of illness? Consider the speed of onset, duration and severity of episodes and any danger posed to self and others.
- Has dosage reduction been attempted before, and, if so, what was the outcome?
- What are the patient's current social circumstances? Is it a period of relative stability, or are stressful life events anticipated?
- What is the social cost of relapse (e.g. is the patient the sole breadwinner for a family)?
- Is the patient/carer able to monitor symptoms, and, if so, will they seek help?

As with first-episode patients, patients, carers and key-workers should be aware of the early signs of relapse and how to access help. Be aware that targeted relapse treatment is much less effective than continuous prophylaxis.[10] Those with a history of aggressive behaviour or serious suicide attempts and those with residual psychotic symptoms should be considered for life-long treatment.

Alternative views

While it is clear that antipsychotics effectively reduce symptom severity and rates of relapse, a minority view is that antipsychotics might also sensitise patients to psychosis. The hypothesis is that relapse on withdrawal can be seen as a type of discontinuation reaction resulting from super-sensitivity of dopamine receptors, although the evidence for this remains uncertain.[57] This phenomenon might explain better outcomes seen in first-episode patients who receive lower doses of antipsychotics, but it also suggests the possibility that the use of antipsychotics might ultimately worsen outcomes. It might also explain the poor outcomes seen with abrupt discontinuation of antipsychotics.[54] This observation in turn leads some to question the validity of long-term studies in which active and successful treatment is abruptly stopped since rebound phenomena and withdrawal reactions may account for at least some of the observed high relapse rates.[58]

The concept of 'super-sensitivity psychosis' was much discussed decades ago[59,60] and has recently seen a resurgence.[57] It is also striking that dopamine antagonists used for non-psychiatric conditions can induce withdrawal psychosis.[61–63] Whilst these theories and observations do not alter recommendations made in this section, they do emphasise the need for using the lowest possible dose of antipsychotic in all patients and the balancing of observed benefit with adverse outcomes including those which might be less clinically obvious (e.g. the possibility of structural brain changes[64]). Clinicians should remain open-minded about the possibility that long-term antipsychotics may worsen, or at least not improve, outcomes in some people with schizophrenia.

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Negative symptoms

Negative symptoms in schizophrenia symptoms represent the absence or diminution of normal behaviours and functions and constitute an important dimension of psychopathology. A subdomain of 'expressive deficits' manifests as a decrease in verbal output or verbal expressiveness and flattened or blunted affect, assessed by diminished facial emotional expression, poor eye contact, decreased spontaneous movement and lack of spontaneity. A second 'avolition/amotivation' subdomain is characterised by a subjective reduction in interests, desires and goals, and a behavioural reduction in purposeful acts, including a lack of self-initiated social interactions.[1,2]

Persistent negative symptoms are held to account for much of the long-term morbidity and poor functional outcome of patients with schizophrenia.[3–6] But the aetiology of negative symptoms is complex, and it is important to determine the most likely cause in any individual case before embarking on a treatment regimen. An important clinical distinction is between primary negative symptoms, which comprise an enduring deficit state, predict a poor prognosis and are stable over time, and secondary negative symptoms, which are consequent upon positive psychotic symptoms, depression or demoralisation, or medication side effects, such as bradykinesia as part of drug-induced parkinsonism.[5,7] Other sources of secondary negative symptoms may include chronic substance/alcohol use, high-dose antipsychotic medication, social deprivation, lack of stimulation and hospitalisation.[8] Secondary negative symptoms may be best tackled by treating the relevant underlying cause. In people with established schizophrenia, negative symptoms are seen to a varying degree in up to three-quarters, with up to 20% having persistent primary negative symptoms.[9,10]

The literature pertaining to the pharmacological treatment of negative symptoms largely consists of sub-analyses of acute efficacy studies, correlational analysis and path analyses.[11] There is often no reliable distinction between primary and secondary negative symptoms or between the two subdomains of expressive deficits and avolition/amotivation, and few studies specifically recruit patients with persistent negative symptoms. While the evidence suggests short-term efficacy for a few interventions, there is no robust evidence for an effective treatment for persistent primary negative symptoms.

In general:

- In first-episode psychosis, the presence of negative symptoms has been related to poor outcome in terms of recovery and level of social functioning.[4,9] There is evidence to suggest that the earlier a psychotic illness is effectively treated, the less likely is the development of negative symptoms over time.[12–14] However, when interpreting such data, it should be borne in mind that an early clinical picture characterised by negative symptoms, being less socially disruptive and more subtle as signs of psychotic illness than positive symptoms, may contribute to delay in presentation to clinical services and thus associated with a longer duration of untreated psychosis. In other words, patients with an inherently poorer prognosis in terms of persistent negative symptoms may be diagnosed and treated later.
- While antipsychotic medication has been shown to improve negative symptoms, this benefit seems to be limited to secondary negative symptoms in acute psychotic episodes.[15] There is no consistent evidence for any superiority of SGAs over FGAs in the

treatment of negative symptoms.[16–20] Similarly, early analyses found no consistent evidence for the superiority of any individual SGA.[21] While a meta-analysis of 38 RCTs found a statistically significant reduction in negative symptoms with SGAs, the effect size did not reach a threshold for 'minimally detectable clinical improvement over time'.[22]

- Nevertheless, a meta-analysis[23] suggests there are robust data suggesting superior efficacy against negative symptoms with certain antipsychotic treatment strategies, such as amisulpride[24–27] and cariprazine,[28,29] and that olanzapine and quetiapine may be more effective than risperidone. Augmentation with aripiprazole may also be effective.[30,31]
- While clozapine remains the only medication with convincing superiority for TRS, whether it has superior efficacy for negative symptoms, at least in the short-term, in such cases remains uncertain.[32–34] One potential confound in studies of clozapine for negative symptoms is that the medication has a low liability for parkinsonian side effects, including bradykinesia, which have a phenomenological overlap with negative symptoms, particularly the subdomain of expressive deficits.
- With respect to non-antipsychotic pharmacological interventions, several drugs that modulate glutamate pathways have been directly tested as adjuncts, but this approach has proved disappointing. Metabotropic glutamate 2/3 (mGlu2/3) receptor agonists have not been found to have any clear effect on negative symptoms over placebo.[35,36] Drugs modulating NMDA receptors in other ways have been tested: for example, there are negative RCTs of glycine,[37] d-serine,[38] modafinil,[39,40] armodafinil,[41] and bitopertin[42,43] augmentation of antipsychotic medication. There is a small preliminary positive RCT of pregnenolone.[44]
- With respect to decreasing glutamate transmission, there are inconsistent meta-analysis findings for lamotrigine augmentation of clozapine[45,46] and one positive[47] and one negative[48] RCT of memantine (the negative study being much larger). There is some suggestion from meta-analyses of relevant studies that adding minocycline, an antibiotic and inflammatory drug, may improve negative symptoms, but the total sample size remains small.[49,50] The BeneMin study was designed to determine whether or not adjunctive minocycline, administered early in the course of schizophrenia, protected against the development of negative symptoms over a year, but the findings did not provide any evidence of clinical benefit with such a strategy.[51]
- With respect to antidepressant augmentation of an antipsychotic for negative symptoms, a Cochrane review concluded that this might be an effective strategy for reducing affective flattening, alogia and avolition,[52] although RCT findings for antidepressant augmentation of antipsychotic medication have found only inconsistent evidence of modest efficacy.[53–56] One meta-analysis of placebo-controlled studies in people with established schizophrenia found that adjunctive antidepressant treatment was associated with a limited reduction in negative symptoms, but only with augmentation of FGAs.[57] Another review of meta-analyses of relevant studies concluded that the evidence suggested a beneficial effect for some SSRIs, such as fluvoxamine, citalopram, and the α2 receptor antagonists mirtazapine and mianserin.[15] Reboxetine may have useful activity.[58]
- Considering glutamate antagonists as adjunctive therapy for negative symptom improvement, there is some limited evidence that topiramate (a noradrenaline

reuptake inhibitor) may have some efficacy for symptom reduction in schizophrenia spectrum disorders, including negative symptoms.[59]

- Meta-analyses support the efficacy of augmentation of an antipsychotic with ginkgo biloba[60] and a COX-2 inhibitor (albeit with a small effect size),[61] while small RCTs have demonstrated some benefit for selegiline,[62,63] pramipexole,[64] topical testosterone,[65] ondansetron[66] and granisetron.[67] The findings from studies of repetitive transcranial magnetic stimulation (rTMS) are mixed but promising.[68–70] The evidence for transcranial direct current stimulation (tDCS) as a treatment for negative symptoms is limited and inconclusive.[15,71] A large (n = 250) RCT in adults[72] and a smaller RCT in elderly patients[73] each found no benefit for donepezil and there is a further negative RCT of galantamine.[74]

Patients who misuse psychoactive substances experience fewer negative symptoms than patients who do not.[75] But rather than any pharmacological effect, it may be that this association at least partly reflects that those people who develop psychosis in the context of substance use, specifically cannabis, have fewer neurodevelopmental risk factors and thus better cognitive and social function.[76,77]

Summary and recommendations

(Derived from the BAP schizophrenia guideline 2020,[78] Veerman et al. 2017,[8] Aleman et al. 2017[15] and Remington et al. 2016[79])

- There are no well-replicated, large trials, or meta-analyses of trials, with negative symptoms as the primary outcome measure that have yielded convincing evidence for enduring and clinically significant benefit.
- Where some improvement has been demonstrated in clinical trials, this may be limited to secondary negative symptoms.
- Psychotic illness should be identified and treated as early as possible as this may offer some protection against the development of negative symptoms.
- For any given patient, the antipsychotic medication that provides the best balance between overall efficacy and adverse effects should be used at the lowest dose that maintains control of positive symptoms.
- Where negative symptoms persist beyond an acute episode of psychosis:
  - Ensure EPS (specifically bradykinesia) and depression are detected and treated if present, and consider the contribution of the environment to negative symptoms (e.g. institutionalisation, lack of stimulation)
  - There is insufficient evidence at present to support a recommendation for any specific pharmacological treatment for negative symptoms. Nevertheless, a trial of add-on medication for which there is some RCT evidence for efficacy, such as an antidepressant, may be worth considering in some cases, ensuring that the choice of the augmenting agent is based on minimising the potential for compounding side effects through pharmacokinetic or pharmacodynamic drug interactions.

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Monitoring

The following table summarises suggested monitoring for those receiving antipsychotic medication.[1] Monitoring of people taking antipsychotics is very poor in most countries.[2–5] Guidance given here is strongly recommended to assure safe use of these drugs. More details, references and background are provided in specific sections in this chapter.

Parameter/ test	Suggested frequency	Action to be taken if results outside reference range	Medications with special precautions	Medications for which monitoring is not required
Urea and electrolytes (including creatinine or estimated GFR)	Baseline and yearly as part of a routine physical health check	Investigate all abnormalities detected	Amisulpride and sulpiride renally excreted – consider reducing dose if GFR reduced	None
Full blood count (FBC)[6–11]	Baseline and yearly as part of a routine physical health check and to detect chronic bone marrow suppression (small risk associated with some antipsychotic medications)	Stop suspect medication if neutrophils fall below 1.5×10^9/L Refer to specialist medical care if neutrophils below 0.5×10^9/L. Note high frequency of benign ethnic neutropenia in certain ethnic groups	Clozapine – FBC weekly for 18 weeks, then two-weekly up to one year, then monthly (schedule varies from country to country)	None
Blood lipids[12,13] (cholesterol; triglycerides) Fasting sample, if possible	Baseline, at 3 months then yearly to detect antipsychotic-induced changes, and generally monitor physical health	Offer lifestyle advice. Consider changing antipsychotic medication and/or initiating statin therapy	Clozapine, olanzapine – 3 monthly for first year, then yearly	Some antipsychotic medications (e.g. aripiprazole, lurasidone) not clearly associated with dyslipidaemia, but prevalence is high in this patient group,[14–16] so all patients should be monitored
Weight[12,13,16] (include waist size and BMI, if possible)	Baseline, frequently for three months then yearly to detect antipsychotic-induced changes, and generally monitor physical health	Offer lifestyle advice. Consider changing antipsychotic medication and/or dietary/ pharmacological intervention	Clozapine, olanzapine – frequently for three months then 3 monthly for first year, then yearly	Aripiprazole, ziprasidone, brexpiprazole, cariprazine and lurasidone not clearly associated with weight gain but monitoring recommended nonetheless – obesity prevalence high in this patient group
Plasma glucose (fasting sample, if possible)	Baseline, at 4–6 months, then yearly to detect antipsychotic-induced changes and generally monitor physical health	Offer lifestyle advice. Obtain fasting sample or non-fasting and HbA_{1c}. Refer to GP or specialist	Clozapine, olanzapine, chlorpromazine – test at baseline, one month, then 4–6 monthly	Some antipsychotic medications not clearly associated with IFG, but prevalence is high in this patient group,[17,18] so all patients should be monitored

(*Continued*)

Parameter/ test	Suggested frequency	Action to be taken if results outside reference range	Medications with special precautions	Medications for which monitoring is not required
ECG[19,20]	Baseline and when target dose is reached (ECG changes rare in practice[21]) on admission to hospital and before discharge if medication regimen changed.	Discuss with/refer to cardiologist if abnormality detected	Haloperidol, pimozide, sertindole – ECG mandatory; ziprasidone – ECG mandatory in some situations	Risk of sudden cardiac death increased with most antipsychotic medications.[22] Ideally, all patients should be offered an ECG at least yearly
Blood pressure	Baseline; frequently during dose titration and dosage changes to detect antipsychotic-induced changes, and generally monitor physical health	If severe hypotension or hypertension (clozapine) observed, slow rate of titration. Consider switching to another antipsychotic if symptomatic postural hypotension. Treat hypertension in line with NICE guidelines	Clozapine, chlorpromazine and quetiapine most likely to be associated with postural hypotension	Amisulpride, aripiprazole, brexpiprazole, cariprazine, lurasidone, trifluoperazine, sulpiride
Prolactin	Baseline, then at 6 months, then yearly to detect antipsychotic-induced changes	Switch medications if hyperprolactinaemia confirmed and symptomatic. Consider tests of bone mineral density (e.g. DEXA scanning) for those with chronically raised prolactin.	Amisulpride, sulpiride, risperidone and paliperidone particularly associated with hyperprolactinaemia	Asenapine, aripiprazole, brexpiprazole, cariprazine, clozapine, lurasidone, quetiapine, olanzapine (<20mg), and ziprasidone usually do not elevate plasma prolactin, but worth measuring if symptoms arise
Liver function tests (LFTs)[23–25]	Baseline, then yearly as part of a routine physical health check and to detect chronic antipsychotic-induced changes (rare)	Stop suspect medication if LFTs indicate hepatitis (transaminases × 3 normal) or functional damage (PT/albumin change)	Clozapine and chlorpromazine associated with hepatic failure	Amisulpride, sulpiride
Creatinine phospho kinase (CPK)	Baseline, then if NMS suspected	See the section on NMS	NMS more likely with high-potency first-generation antipsychotic medications	None

Other tests: Patients on clozapine may benefit from an **EEG,**[26,27] as this may help determine the need for anticonvulsant treatment (although interpretation is obviously complex). Those on quetiapine should have **thyroid** function tests yearly, although the risk of abnormality is very small.[28,29]

Key: DEXA, dual-energy X-ray absorptiometry; NMS, neuroleptic malignant syndrome; PT, prothrombin time; BMI – body mass index; ECG – electrocardiograph; EEG – electroencephalogram; GFR – glomerular filtration rate; IFG – impaired fasting glucose.

Note: This table is a summary – see individual sections for detail and discussion.

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Relative adverse effects – a rough guide

Drug	Sedation	Weight gain	Akathisia	Parkinsonism	Anti-cholinergic	Hypotension	Prolactin elevation
Amisulpride*	–	+	+	+	–	–	+++
Aripiprazole	–	–	+	–	–	–	–
Asenapine*	+	+	+	–	–	–	+
Benperidol*	+	+	+	+++	+	+	+++
Brexpiprazole*	–	–	–	–	–	–	–
Cariprazine*	–	–	+	–	–	–	–
Chlorpromazine	+++	++	+	++	++	+++	+++
Clozapine	+++	+++	–	–	+++	+++	–
Flupentixol*	+	++	++	++	++	+	+++
Fluphenazine*	+	+	++	+++	+	+	+++
Haloperidol	+	+	+++	+++	+	+	++
Iloperidone*	–	++	+	+	–	+	–
Lumateperone*	++	–	–	–	–	–	–
Loxapine*	++	+	+	+++	+	++	+++
Lurasidone	+	–	+	+	–	–	–
Olanzapine	++	+++	–	–	+	+	+
Paliperidone	+	++	+	+	+	++	+++
Perphenazine	+	+	++	+++	+	+	+++
Pimavanserin*	-	-	-	-	-	-	-
Pimozide*	+	+	+	+	+	+	+++
Pipothiazine*	++	++	+	++	++	++	+++
Promazine*	+++	++	+	+	++	++	++
Quetiapine	++	++	–	–	+	++	–
Risperidone	+	++	+	+	+	++	+++
Sertindole*	–	+	+	–	–	+++	–
Sulpiride*	–	+	+	+	–	–	+++
Trifluoperazine	+	+	+	+++	+	+	+++
Ziprasidone*	+	–	+	–	–	+	+
Zuclopenthixol*	++	++	++	++	++	+	+++

Key: *Availability varies from country to country; +++ High incidence/severity; ++ Moderate; + Low; – Very low.

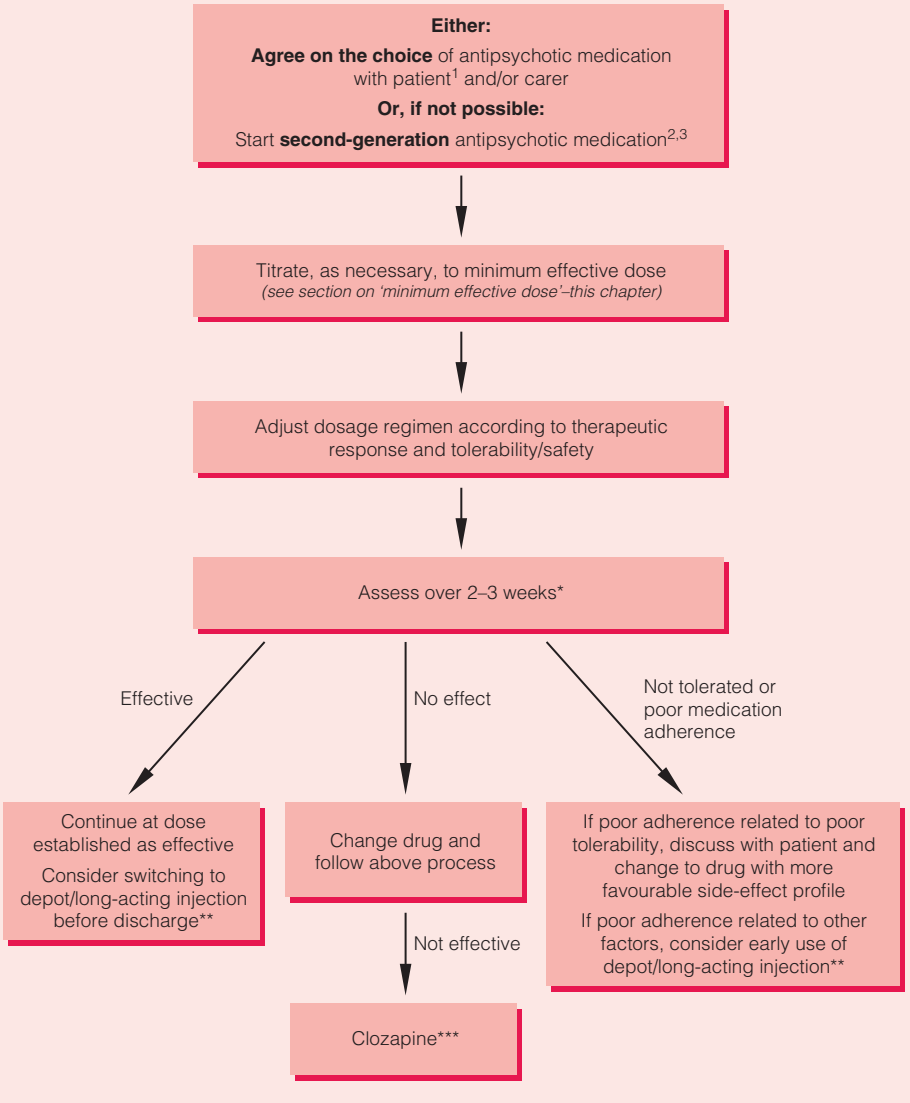
Note: The table notes approximate estimates of relative incidence and/or severity, based on clinical experience, manufacturers' literature and published research. This is a very rough guide – see individual sections for more precise and referenced information.

Other adverse effects not mentioned in this table do occur. Please see dedicated sections on other adverse effects included in this book for more information.

Treatment algorithms for schizophrenia

First-episode schizophrenia

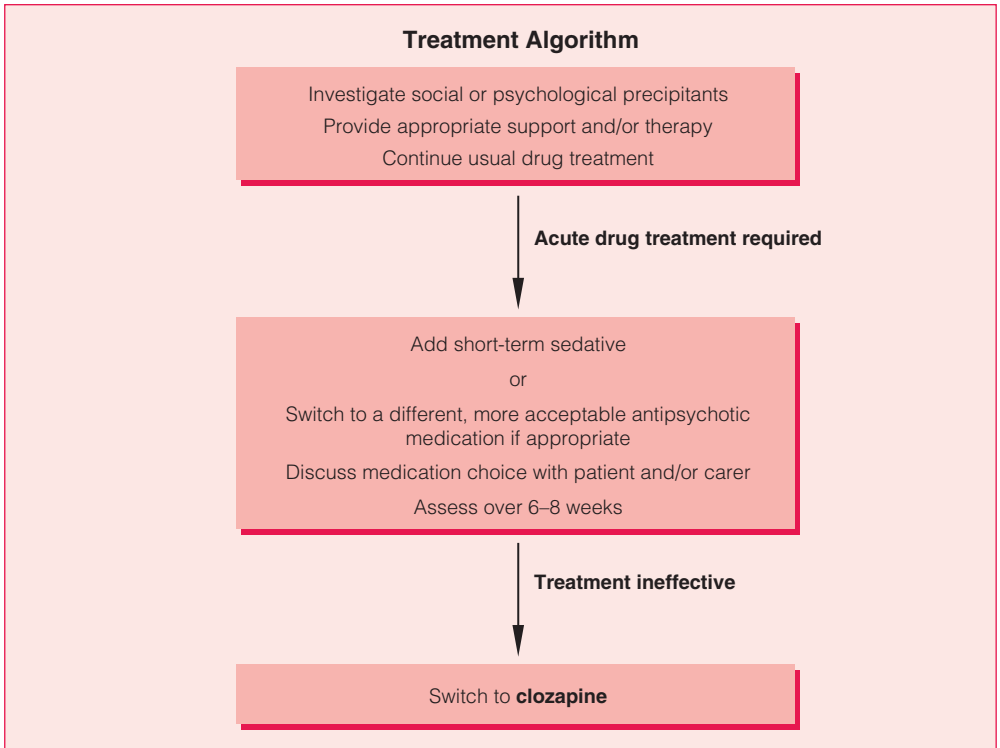
Treatment algorithm



* Any improvement is likely to be apparent within 2–3 weeks of receiving an effective dose.[4] Most improvement occurs during this period.[5] If no effect by 2–3 weeks, change dose or drug. If some response detected, continue for a total of 10 weeks before abandoning treatment.[6]
** Relapse and readmission rates are vastly reduced by early use of depot/long-acting injections in this patient group.[7–9] First episode patients will accept long-acting injections.[10]
*** Early use of clozapine much more likely than anything else to be successful.[6,11]
Reluctance to use clozapine is associated with poor outcomes.[12]

Relapse or acute exacerbation of schizophrenia

(full adherence to medication confirmed)

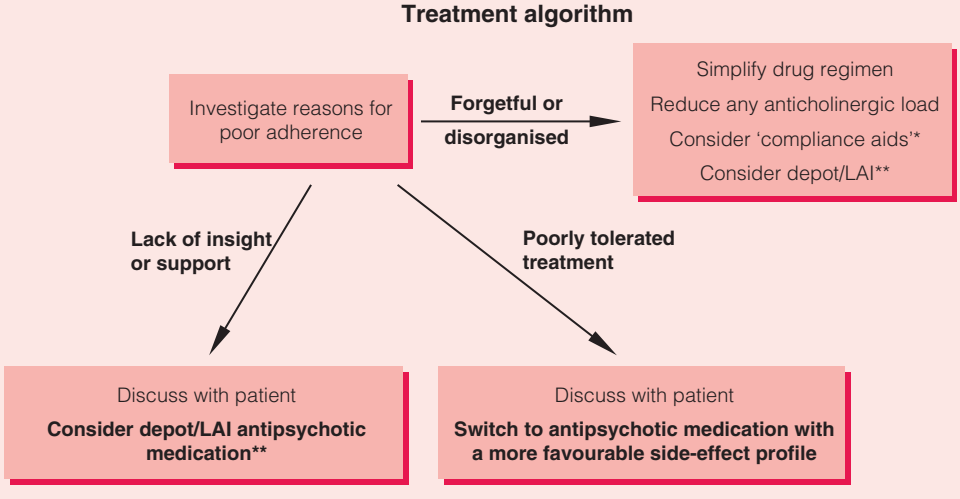


Notes

- First-generation drugs may be slightly less efficacious than some SGAs.[13,14] FGAs should probably be reserved for second-line use (or not used at all) because of the possibility of poorer outcome compared with SGAs and the higher risk of movement disorder, particularly tardive dyskinesia[15,16]
- Choice should be based largely on comparative adverse effect profile and relative toxicity. Patients seem able to make informed choices based on these factors,[17,18] although in practice they have in the past only very rarely been involved in drug choice.[19] Allowing patients informed choice seems to improve outcomes.[1]
- Where there is prior treatment failure (but not confirmed treatment refractoriness), olanzapine or risperidone may be better options than quetiapine.[20] Olanzapine, because of the wealth of evidence suggesting slight superiority over other antipsychotics, should probably be tried before clozapine unless contra-indicated.[21–24] Note, however, that one RCT[6] found continuing with amisulpride was as effective as switching to olanzapine.
- Before considering clozapine, ensure adherence to prior therapy using depot/LAI formulation or plasma drug level monitoring of oral treatment. Most non-adherence is undetected in practice,[23,25] and apparent treatment resistance may simply be a result of inadequate treatment.[26]
- Time to response is increased, and total response decreased in exacerbation of multi-episode schizophrenia[27]
- Where there is confirmed treatment resistance (failure to respond to adequate trials of at least two antipsychotic medications), evidence supporting the use of clozapine (and only clozapine) is overwhelming[28,29]

Relapse or acute exacerbation of schizophrenia

(adherence doubtful or known to be poor)



*Compliance aids (e.g. Medidose system in the UK) are not a substitute for patient education. The ultimate aim should be to promote independent living, perhaps with patients filling their own compliance aid, having first been given support and training. Note that such compliance aids are of little use unless the patient is clearly motivated to adhere to prescribed treatment. Note also that some medicines are not suitable for storage in compliance aids.

**Patients generally have positive views of depot medication.[10,30]

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First-generation antipsychotics – place in therapy

Nomenclature

First-generation ('typical') and second-generation ('atypical') antipsychotic medications are not categorically differentiated, the medications in both groups being heterogeneous in terms of pharmacological and side-effect profiles. First-generation medications were introduced before 1990 and tend to be associated with acute EPS, hyperprolactinaemia and, in the longer term, tardive dyskinesia (TD). There are expectations that such adverse effects are less likely or absent with second-generation antipsychotic medications (introduced after 1990), although in practice most show dose-related EPS, some induce hyperprolactinaemia (often to a greater extent than with FGAs) and all will give rise to TD, albeit at a lower incidence than FGAs. Second-generation medications tend to be associated with metabolic and cardiac complications,[1–3] although this is *not* true of all SGAs and it *is* true of some FGAs. To complicate matters further, it has been suggested that the therapeutic and adverse effects of FGAs can be separated by careful dosing[4] – essentially turning FGAs into SGAs if used in small enough doses (although there is much evidence to the contrary[5–7]).

Given these observations, it seems unwise and unhelpful to consider so-called FGAs and SGAs as distinct groups of drugs. Perhaps the essential difference between the two groups is the size of the therapeutic index in relation to acute EPS. For instance, haloperidol has an extremely narrow range of doses at which it is effective but does not cause extrapyramidal side effects (EPSE) (perhaps 4.0 to 4.5mg/day), whereas olanzapine has a wide range of therapeutic doses (5–40mg/day) at which it does not generally cause EPSE.

The use of Neuroscience-based Nomenclature (NbN)[1,2] (for which there is a free app for iPhone and other devices) obviates the need for classification into an FGA or SGA and describes individual drug by their pharmacological activity. The wider use of NbN will undoubtedly improve understanding of individual drug effects and perhaps forestall future redundant categorisation.

Role of older antipsychotics

FGAs still play an important role in schizophrenia. For example, chlorpromazine and haloperidol are frequent choices for PRN ('when necessary') medication and depot preparations of haloperidol, zuclopenthixol and flupentixol are commonly prescribed. FGAs can offer a valid alternative to SGAs where SGAs are poorly tolerated (usually because of metabolic changes) or where FGAs are preferred by patients themselves. Some FGAs may be less effective than some non-clozapine SGAs (amisulpride, olanzapine and risperidone may be slightly more efficacious[3,4]), but any differences in therapeutic efficacy seem to be modest. Two large pragmatic studies, CATIE[8] and CUtLASS,[5] found few important differences between SGAs and FGAs (mainly perphenazine and sulpiride, respectively).

The main drawbacks of FGAs are, inevitably, acute EPS, hyperprolactinaemia and TD. Hyperprolactinaemia is probably unavoidable in practice (the dose that achieves efficacy is too close to the dose that causes hyperprolactinaemia) and, even when not symptomatic, hyperprolactinaemia may grossly affect hypothalamic function.[6] It is also associated with sexual dysfunction,[7] but be aware that the autonomic effects of some

SGAs may also cause sexual dysfunction.[8] Also, some SGAs (risperidone, paliperidone, amisulpride) increase prolactin to a greater extent than FGAs.[9]

All FGAs are potent dopamine antagonists, which are liable to induce dysphoria.[10] Perhaps as a consequence, some FGAs may produce smaller benefits in quality of life than some SGAs.[11]

TD very probably occurs more frequently with FGAs than SGAs[12–15] (notwithstanding difficulties in defining what is 'atypical'), although there remains some uncertainty[15–17] and the dose of FGA used is a crucial factor. Amongst SGAs, partial agonists may have the lowest risk of TD.[18] Careful observation of patients and the prescribing of the lowest effective dose are essential to help reduce the risk of this serious adverse event.[19,20] Even with these precautions, the risk of TD with some FGAs may be unacceptably high.[21]

A good example of the relative merits of SGAs and a carefully dosed FGA comes from a trial comparing paliperidone palmitate with low-dose haloperidol decanoate.[22] Paliperidone produced more weight gain and prolactin change, but haloperidol was associated with significantly more frequent akathisia and parkinsonism, and, numerically, a higher incidence of TD. Efficacy was identical.

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NICE guidelines for the treatment of schizophrenia[1]

The 2009 NICE Guidelines[1] differed importantly from previous guidelines. There was no longer an imperative to prescribe an 'atypical' as first-line treatment, and it was recommended only that clozapine be 'offered' (rather than prescribed) after the prior failure of two antipsychotics. These semantic differences pointed respectively towards a disillusionment with SGAs and a recognition of the delay in prescribing clozapine in practice. Much emphasis was placed on involving patients and their carers in prescribing decisions. There is some evidence that this is rarely done[2] but that it can be done.[3] New NICE Guidelines appeared in February 2014 and were reviewed again in March 2019.

NICE Guidelines – a summary

- For people with newly diagnosed schizophrenia, offer oral antipsychotic medication as well as psychological interventions (CBT or family intervention). Provide information and discuss the benefits and side-effect profile of each drug with the service user. The choice of drug should be made by the service user and healthcare professional together, considering:
  - the relative potential of individual antipsychotic drugs to cause extrapyramidal side effects (including akathisia), cardiovascular side effects, metabolic side effects (including weight gain), hormonal side effects (including raised prolactin levels) and other side effects (including unpleasant subjective experiences);
  - the views of the carer where the service user agrees.
- Before starting antipsychotic medication, undertake and record the following baseline investigations:
  - Weight
  - Waist circumference
  - Pulse and blood pressure
  - Fasting blood glucose, HbA_{1C}, blood lipid profile, prolactin
  - Assessment of movement disorders
  - Assessment of nutritional status, diet and level of physical activity
- Before starting antipsychotic medication, offer the person with schizophrenia an electrocardiogram (ECG) if:
  - specified in the SPC
  - a physical examination has identified specific cardiovascular risk (such as diagnosis of high blood pressure)
  - there is personal history of cardiovascular disease, or
  - the service user is being admitted as an inpatient.
- Treatment with antipsychotic medication should be considered an explicit individual therapeutic trial, and the following should be considered:
  - Recording of indications and expected benefits and risks of oral antipsychotic medication, and the expected time for a change in symptoms and appearance of side effects.
  - At the start of treatment, give a dose at the lower end of the licensed range and slowly titrate upwards within the dose range given in the British National Formulary (BNF) or SPC.

  - Justify and record reasons for dosages outside the range given in the BNF or SPC.
  - Record the rationale for continuing, changing or stopping medication and the effects of such changes.
  - Carry out a trial of medication at optimum dosage for 4–6 weeks (although half of this period is probably sufficient if no effect at all is seen).
- Monitor and record the following regularly and systematically throughout treatment, but especially during titration:
  - efficacy, including changes in symptoms and behaviour
  - side effects of treatment, taking into account overlap between certain side effects and clinical features of schizophrenia, for example, the overlap between akathisia and agitation or anxiety
  - adherence
  - weight, weekly for the first 6 weeks, then at 12 weeks, 1 year and annually
  - waist circumference annually
  - pulse and blood pressure at 12 weeks, 1 year and annually
  - fasting blood glucose, HbA_{1C} and blood lipids at 12 weeks, 1 year and annually
  - nutritional status, diet and physical activity.
- Physical monitoring is to be the responsibility of the secondary care team for one year or until the patient is stable.
- Discuss the use of alcohol, tobacco, prescription and non-prescription medication as well as the use of illicit drugs with the service user and carer if appropriate. Discuss their potential interactions with the prescribed therapy and psychological treatments.
- Do not use a loading dose of antipsychotic medication (often referred to as 'rapid neuroleptisation') (Note that this does not apply to loading doses of depot forms of olanzapine and paliperidone).
- Do not routinely initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication).
- If prescribing chlorpromazine, warn of its potential to cause skin photosensitivity. Advise using sunscreen if necessary.
- Consider offering depot/long-acting injectable antipsychotic medication to people with schizophrenia:
  - who would prefer such treatment after an acute episode
  - in patients known to be non-adherent to oral treatment and/or those who prefer this method of administration.
- Offer clozapine to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs alongside psychological therapies. The misuse of illicit substances (including alcohol) and the use of other prescribed medication or physical illness should be excluded. At least one of the drugs should be a non-clozapine second-generation antipsychotic. (See section Treatment Algorithms for schizophrenia – we recommend that one of the drugs should be olanzapine)
- For people with schizophrenia whose illness has not responded adequately to clozapine at an optimised dose, healthcare professionals should establish prior compliance with optimised antipsychotic treatment (including measuring drug levels) and engagement with psychological treatment before adding a second antipsychotic to augment

treatment with clozapine. An adequate trial of such an augmentation may need to be up to 8–10 weeks (some data suggest 6 weeks may be enough[4]). Choose a drug that does not compound the common side effects of clozapine.

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Antipsychotic response – to increase the dose, to switch, to add or just wait – what is the right move?

For any clinician actively involved in the care of people with schizophrenia, the single most common clinical dilemma is what to do when treatment with the current antipsychotic medication seems to be suboptimal. This may be for two broad reasons: first, while the symptoms are well controlled the side effects are problematic and, secondly, there is an inadequate therapeutic response. Fortunately, with regard to the first reason, the diversity of the available antipsychotic medications means that it is usually possible to find one that has a side-effect profile that is more appropriate and more tolerable. With regard to the second reason – an inadequate symptom response – what to do next is a more difficult question. If the illness has not shown sufficient improvement despite serial, adequate trials, in terms of dosage, duration and adherence, of two antipsychotic medications, then a trial of clozapine should be considered. However, should the person be reluctant to try clozapine, the clinician has four main choices: to increase the dose of the current medication; to switch to another antipsychotic medication; to add an adjunctive medication, or just to monitor the illness in the hope that changing external factors allow recovery.

When to increase the dose?

While optimal doses of FGAs were always a matter of debate, the recommended doses of the SGAs were generally based on careful and extensive clinical trials. Despite this, the consensus on optimal SGA dosages has changed over time. For example, when risperidone was first launched, it was suggested that optimal titration was from 2mg to 4mg to 6mg or more for all patients. However, subsequently clinical practice moved towards the use of lower doses.[1] On the other hand, when quetiapine was introduced, 300mg was considered the optimal dose. The overall consensus now is towards higher doses,[2] although RCT and other evidence do not support this shift.[2,3] Nonetheless, most clinicians feel comfortable in navigating within the recommended SGA clinical dose ranges. The more critical question is what should be done if the upper limit of the dose range has been reached and, while the individual is tolerating the medication well, there is only limited benefit.

Dose–response observations

Davis and Chen[4] performed a systematic meta-analysis of relevant dose–response data available up to 2004 and concluded that the average dose that produces maximal benefit was 4mg for risperidone, 16mg of olanzapine, 120mg of ziprasidone and 10–15mg of aripiprazole (they could not determine such a dose for quetiapine using their method).[4] More recent trials have tried to compare 'high-dose' with standard dosage. For example, one group[5] studied the dose–response relationship of standard and higher doses of olanzapine in a randomised, double-blind, 8-week, fixed-dose study comparing olanzapine 10mg, 20mg and 40mg. While no additional benefit was found with the higher doses (i.e. 40mg was no better than 10mg), there was clear evidence for an increasing side-effect burden (weight gain and raised plasma prolactin level). Similarly, the initial licensing studies of risperidone compared the usual doses of 2–6mg with higher doses of 8–16mg/day. There was no additional benefit with the higher doses but

a clear signal for a greater risk of side effects (EPS and raised plasma prolactin). The findings of these studies are in accord with older studies involving fixed doses of haloperidol,[6] where 8mg/day is clearly the dose above which no additional benefit is seen.[7]

Nonetheless, it is important to keep in mind that these doses are extracted from group evidence where patients are assigned to different doses, which is a different situation from the clinical one where the prescriber considers increasing the dose only in those patients whose illnesses have failed to respond to the initial dosage regimen. Kinon et al.[8] examined patients who failed to respond to the (then) standard dose of fluphenazine (20mg) and tested three strategies: increasing the dose to 80mg, switching to haloperidol or watchful waiting (on the original dose). All three strategies proved to be equivalent in terms of efficacy. These findings provide little supportive evidence at a group level (as opposed to an individual level) for treatment beyond the recommended dose range. Such RCT evidence is corroborated by the clinical practice norms – Hermes and colleagues examined the CATIE data to identify clinical factors that predicted a prescriber's decision to increase the dose and found that decisions for dose change (within the therapeutic ranges) were only weakly associated with clinical measures.[9] More recently, a trial of lurasidone[10] in adult patients with schizophrenia showed that following a lack of response after two weeks on lurasidone 80mg/d, a dose increase to 160mg/d was associated with significant symptom improvement compared with continuing on lurasidone 80mg/d. However, this result may not be generalisable to other antipsychotic medications.

A 2018 Cochrane systematic review of relevant studies concluded that there was no good-quality evidence that for illness not responding to initial antipsychotic treatment, there was any difference between increasing the antipsychotic dose and continuing antipsychotic treatment at the same dose.[11]

Plasma level variations

Group level evidence cannot completely determine individual treatment decisions. There are significant inter-individual variations in plasma drug levels in patients treated with antipsychotic medication. One can often encounter a patient who, when receiving medication at the higher end of the dose range (say 6mg of risperidone or 20mg of olanzapine), would have plasma drug levels that are well below the range expected for 2mg risperidone or 10mg of olanzapine, and these levels may not reach the threshold for response. In such patients, a rational case could be made for increasing the dose, provided the patient is informed, and the side effects are tolerable, to bring the plasma levels to the optimal range for the particular medication. More details on plasma levels and their interpretation are provided in Chapter 11. However, what are the treatment possibilities when a lack of therapeutic response is encountered despite the patient's adherence to their medication regimen, the prescription of a dosage at the top of the recommended range, and apparently sufficient plasma levels?

Treatment choices

There are essentially three options here, a trial of clozapine, switch to another antipsychotic medication or add another (non-clozapine) antipsychotic medication. If the patient meets the criteria for clozapine treatment, this is undoubtedly the preferred option. Yet, in a clinical audit of community (not inpatient) practice in the UK, covering

some 5000 patients in 60 different NHS Trusts, it was found that 40% of the patients whose illnesses met the criteria for treatment-resistant schizophrenia had not received clozapine. For the vast majority (85%) of those who had started clozapine, this had been delayed after the failure of two serial trials of antipsychotic medication for much longer than is advised in most guidelines.[12]

Some patients may be averse to the mandatory regular blood testing, the side effects and the regular appointments required as part of the clozapine regimen. In such patients, the options are switching to another antipsychotic medication or to add one. The data on switching are sparse. While almost every clinical trial in patients with established schizophrenia has entailed the patient switching from one antipsychotic medication to another, there are no rigorous studies addressing preferred medication switches (e.g. if risperidone fails – what next? olanzapine, quetiapine, aripiprazole or ziprasidone). If one looks at only the switching trials which have been sponsored by the drug companies – it leads to a rather confusing picture, with the trial results being very closely linked to the sponsors' interest (see Heres S, et al. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics[13]).

CATIE, the major US-based publicly funded comparative trial, examined patients who had failed their first SGA and were then randomly assigned to a different second one[14] – patients switched to olanzapine and risperidone did better than those switched to quetiapine and ziprasidone. This greater effectiveness is supported by a meta-analysis that compared a number of SGAs with FGAs and concluded that other than clozapine, only amisulpride, risperidone and olanzapine were superior to FGAs in efficacy;[15] and a meta-analysis comparing SGAs amongst themselves suggested that olanzapine and risperidone (in that order) may be modestly more effective than the others.[16] Nevertheless, if a patient has not yet tried olanzapine or risperidone, it would be a reasonable decision to switch to these medications provided the side-effect balance is favourable. Comparing these two medications – the data are somewhat limited. However, a number of controlled, but open-label studies do show an asymmetrical advantage (i.e. switching to olanzapine being more effective, than to risperidone) – providing some direction, albeit incomplete.[17,18]

The best medication regimen (aside from clozapine) to choose for a patient who fails on olanzapine and risperidone remains unclear. Should one switch to, say, aripiprazole or ziprasidone or even an older FGA, or should another antipsychotic medication be added? Interestingly, studies that have switched patients to aripiprazole for reasons of tolerability (weight gain, etc.) either find no loss of efficacy[19,20] or an improvement in symptom severity after switching.[21,22] The switching method is vitally important, with add-on switching (establishing the dose of aripiprazole before withdrawing the former drug) and cross-tapering giving substantially better outcomes than stop-start.[21]

After 'switching', adding another antipsychotic is probably the most common clinical strategy chosen, as 39–43% of patients in routine care are prescribed more than one antipsychotic.[23] Often, a second antipsychotic is added for additional properties (e.g. quetiapine for sedation or aripiprazole to decrease plasma prolactin – these matters are discussed elsewhere). We are concerned here solely with the use of combined antipsychotic medications to increase efficacy. From a theoretical point of view, since all antipsychotic medications block D_2 receptors (unlike, say, anti-hypertensives which use different mechanisms), there is a limited rationale for addition. Studies of add-ons have

often chosen combinations of convenience or based on clinical lore and perhaps the most systematic evidence is available for the addition of a second antipsychotic to clozapine[24,25] – perhaps supported by the rationale that since clozapine has relatively low D_2 occupancy, increasing its D_2 occupancy may yield additional benefits.[26] However, a meta-analysis of RCTs comparing augmentation with a second antipsychotic with continuing antipsychotic monotherapy in schizophrenia[27] found a lack of double-blind/high-quality evidence for efficacy for the combination, in terms of treatment response and symptom improvement. Furthermore, compared with antipsychotic monotherapy, combined antipsychotics seem to be associated with an increased side-effect burden and a greater risk of high-dose prescribing.[28,29]

While augmentation with another antipsychotic medication as a treatment strategy should probably be avoided, under some conditions of acute exacerbation or agitation the prescriber may see this as the only practicable solution. Or quite often the prescriber may inherit the care of a patient on antipsychotic polypharmacy. Most RCT evidence suggests that such a regimen can be safely switched back to antipsychotic monotherapy without symptom exacerbation, at least in the majority of patients,[30–32] although this is not a universal finding.[33] Essock et al.[32] conducted a relatively large trial involving 127 patients with schizophrenia who were stable on antipsychotic polypharmacy. Over a 12-month period, a switch to monotherapy was successful in about two thirds of the patients in whom it was tested. And in those cases where the move to monotherapy resulted in a return of symptoms, the most common recourse was a return to the original polypharmacy; this was achieved without any significant worsening in this group. The advantages for the monotherapy group were exposure to less medication, equivalent symptom severity and some loss of weight.

So when should the prescriber just continue with the current regimen? The evidence reviewed above suggests that no one strategy, such as increasing the dose, switching to another antipsychotic medication or augmentation with a second antipsychotic medication, is the clear winner in all situations. But increasing the dose if plasma drug levels are low, switching to olanzapine or risperidone if these medications have not been tried, or augmentation if there is insufficient response to clozapine, may be beneficial in some cases. Given the limited efficacy of these manoeuvres, perhaps an equally important call by the treating doctor is when to just stay with the current pharmacotherapy and focus on non-pharmacological means: engagement in case management, targeted psychological treatments and vocational rehabilitation as means of enhancing patient well-being. While it may seem a passive option – staying may often do less harm that aimless switching.

Summary

When treatment fails

- If the dose of antipsychotic medication has been optimised, consider watchful waiting.
- Consider increasing the antipsychotic dose according to tolerability and plasma levels (little supporting evidence[34,35]).
- If this fails, consider switching to olanzapine or risperidone (if not already used).
- If this fails, use clozapine (supporting evidence very strong).
- If clozapine fails, use time-limited augmentation strategies (supporting evidence variable).

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Acutely disturbed or violent behaviour

Acute behavioural disturbance can occur in the context of psychiatric illness, physical illness, substance abuse or personality disorder. Psychotic symptoms are common and the patient may be aggressive towards others secondary to persecutory delusions or auditory, visual or tactile hallucinations. This section deals with behavioural disturbance in the context of severe mental illness. Excited/agitated delirium caused by illicit substance misuse is dealt with in Chapter 9.

The clinical practice of rapid tranquillisation (RT) is used when appropriate psychological and behavioural approaches have failed to de-escalate acutely disturbed behaviour. It is, essentially, a treatment of last resort. Patients who require RT are often too disturbed to give informed consent and therefore participate in randomised controlled trials (RCTs), but with the use of a number of creative methodologies, the evidence base with respect to the efficacy and tolerability of pharmacological strategies has grown substantially in recent years. A comprehensive and up-to-date consensus guideline has been published[1] and, more recently, a systematic review and meta-analysis.[2]

Oral/inhaled treatment

Several studies supporting the efficacy of oral SGAs have been conducted.[3–6] The level of behavioural disturbance exhibited by the patients in these studies was moderate at most, and all subjects accepted oral treatment (this degree of compliance would be unusual in clinical practice). Patients recruited to these studies received the SGA as antipsychotic monotherapy. The efficacy and safety of adding a second antipsychotic as a 'when necessary' treatment has not been explicitly tested in formal RCTs.

A single-dose RCT showed sublingual asenapine to be more effective than placebo for acute agitation.[7] The efficacy of inhaled loxapine in behavioural disturbance that is moderate in severity is also supported by RCTs[8–10] and case series.[11,12] The use of this preparation requires the co-operation of the patient, and bronchospasm is an established but rare side effect.

Parenteral treatment

Large, placebo-controlled RCTs support the efficacy of IM preparations of olanzapine, ziprasidone and aripiprazole. When considered together, these trials suggested that IM olanzapine is more effective than IM haloperidol which in turn is more effective than IM aripiprazole, which itself is more effective than ziprasidone.[2,13] The level of behavioural disturbance in these studies was moderate at most and differences between treatments small.

A large observational study supports the efficacy and tolerability of IM olanzapine in clinical emergencies (where disturbance was severe).[14] A study comparing IM haloperidol with a combination of IM midazolam and IM haloperidol found the combination more effective than haloperidol alone for controlling agitation in palliative care patients.[15]

Several RCTs have investigated the effectiveness of parenteral medication in 'real-life' acutely disturbed patients. Overall:

- Compared with IV midazolam alone, a combination of IV olanzapine or IV droperidol with IV midazolam was more rapidly effective and resulted in fewer subsequent doses of medication being required.[16]
- IM midazolam 7.5–15mg was more rapidly sedating than a combination of haloperidol 5–10mg and promethazine 50mg (TREC 1).[17]
- Olanzapine 10mg was as effective as a combination of haloperidol 10mg and promethazine 25–50mg in the short term, but the effect did not last as long (TREC 4).[18]
- A combination of haloperidol 5–10mg and promethazine 50mg was more effective and better tolerated than haloperidol 5–10mg alone (6% of patients had an acute dystonic reaction) (TREC 3).[19]
- A combination of haloperidol 10mg and promethazine 25–50mg was more effective than lorazepam 4mg (TREC 2).[20]
- A combination of IM chlorpromazine 100mg, haloperidol 5mg and promethazine 25mg was no better than IM haloperidol 5mg plus promethazine 25mg (TREC Lebanon).[21]
- A combination of IV midazolam and IV droperidol was more rapidly sedating than either IV droperidol or IV olanzapine alone. Fewer patients in the midazolam-droperidol group required additional medication doses to achieve sedation.[22]
- IM olanzapine was more effective than IM aripiprazole in the treatment of agitation in schizophrenia in the short term (at 2 hours), but there was no significant difference between treatments at 24 hours.[23]
- IM midazolam 5mg was faster acting and more effective than olanzapine 10mg, ziprasidone 20mg and both 5 and 10mg haloperidol in a large (n = 737) Emergency Room study.[24]
- In an open-label study, the combination of IM haloperidol and IM lorazepam was found to be similar in efficacy to IM olanzapine.[25]
- IM droperidol and IM haloperidol were equally effective.[26]

Cochrane concluded that haloperidol alone is effective in the management of acute behavioural disturbance but poorly tolerated, and that co-administration of promethazine (but not lorazepam) improves tolerability.[27,28] However, NICE considers the evidence relating to the use of promethazine for this purpose to be inconclusive.[29] When assessing haloperidol plus promethazine, Cochrane concluded that the combination is effective for use in patients who are aggressive due to psychosis, and its use is based on good evidence. The resumption of aggression and need for further injections was more likely with olanzapine than with the haloperidol–promethazine combination. The authors also stated that 'haloperidol used on its own without something to offset its frequent and serious adverse effects does seem difficult to justify'.[30] Cochrane concluded that available data for aripiprazole are rather poor. This evidence suggests that aripiprazole is more effective than placebo and haloperidol alone, but not olanzapine. However, caution is advised when generalising these results to real-world practice.[31]

A systematic review and meta-analysis of IM olanzapine for agitation found IM olanzapine and IM haloperidol to be equally effective, but IM olanzapine was associated with a lower incidence of EPSEs.[32] Cochrane suggests that droperidol is effective and may be used to control people with very disturbed and aggressive behaviours caused by psychosis.[33] Droperidol is seeing a resurgence in use in some countries having

become available again (its initial withdrawal was voluntary, so reintroduction is not prohibited).

In a meta-analysis that examined the tolerability of IM antipsychotics when used for the treatment of agitation, the incidence of acute dystonia with haloperidol was reported to be 5%, with SGAs performing considerably better.[34] Acute EPS may adversely affect longer-term compliance.[35] In addition, the formal prescribing information in most countries for haloperidol calls for a pre-treatment ECG[36,37] and recommends that concomitant antipsychotics are not prescribed. The mean increase in QTc after 10mg IM haloperidol can be up to 15ms, but the range is wide.[38]

Note that promethazine may inhibit the metabolism of haloperidol;[39] a pharmacokinetic interaction that is potentially clinically significant given the potential of haloperidol to prolong QTc. While this is unlikely to be problematic if a single dose is administered, repeat dosing may confer risk.

Droperidol is also associated with QT changes (the reason for its past withdrawal). In an observational study set in hospital emergency departments, of the 1009 patients administered parenteral droperidol only 13 patients (1.28%) had an abnormal QT recorded after dose administration. In 7 of these cases another contributory factor was identified. There were no cases of torsades de pointes.[26] In all RT studies of IM droperidol, the overall rate of QT > 500ms was less than 2%.[2]

Intravenous treatment is now rarely used in RT but where benefits are thought to outweigh risks it may be considered as a last resort. A small study comparing high dose IV haloperidol with IV diazepam found both drugs to be effective at 24 hours.[40] Two large observational studies have examined the safety of IV olanzapine when used in the emergency department. The indications for its use varied: agitation being the most common. In one study,[41] in the group treated for agitation (n = 265), over a third of patients required an additional sedative dose after the initial IV olanzapine dose. Hypoxia was reported in 17.7% of cases and supplemental oxygen was used in 20.4% cases. Six patients required intubation (two of these because of olanzapine treatment). In the other study,[42] IV olanzapine (n = 295) was compared with IM olanzapine (n = 489). Additional doses were not required for 81% of patients in the IV group and 84% of patients in the IM group. Respiratory depression was more commonly observed in the group receiving IV olanzapine. Five patients in the IM group and two in the IV group required intubation.

In an acute psychiatric setting, high dose sedation (defined as a dose of more than 10mg of haloperidol, droperidol or midazolam) was not more effective than lower doses but was associated with more adverse effects (hypotension and oxygen desaturation).[43] Consistent with this, a small RCT supports the efficacy of low dose haloperidol, although both efficacy and tolerability were superior when midazolam was co-prescribed.[44] These data broadly support the use of standard doses in clinical emergencies, but the need for further physical restraint after lower doses needs to be considered.

A small observational study supports the effectiveness of buccal midazolam in a PICU setting.[45] Parenteral administration of midazolam, particularly in higher doses, may cause over-sedation accompanied by respiratory depression.[46] Lorazepam IM is an established treatment and TREC 2[20] supports its efficacy, although combining all results from the TREC studies suggests midazolam 7.5–15mg is probably more effective. A Cochrane review of benzodiazepines for psychosis-induced aggression and agitation

concluded that most trials were too small to highlight differences in either positive or negative effects and whilst adding a benzodiazepine to another drug may not be clearly advantageous it may lead to unnecessary side effects.[47]

With respect to those who are behaviourally disturbed secondary to acute intoxication with alcohol or illicit drugs, there are fewer data to guide practice. A large observational study of IV sedation in patients intoxicated with alcohol found that combination treatment (most commonly haloperidol 5mg and lorazepam 2mg) was more effective and reduced the need for subsequent sedation than either drug given alone.[48] A case series ($N = 59$) of patients who received modest doses of oral, IM or IV haloperidol to manage behavioural disturbance in the context of PCP consumption, reported that haloperidol was effective and well tolerated (one case each of mild hypotension and mild hypoxia).[49] A section on the treatment of agitated delirium is included in Chapter 9.

Ketamine is widely used for agitation from hospital emergency departments. In a systematic review of 18 studies of ketamine,[50] a mean dose of 315mg IM ketamine achieved adequate sedation in an average of 7.2 minutes. Over 30% of 650 patients were eventually intubated and more than 1% experienced laryngospasm. Ketamine is probably not an option for RT where facilities for intubation are not available.

Overall the current broad consensus is that midazolam and droperidol are the fastest-acting single drug, intramuscular treatments[51] and that haloperidol alone should be avoided and perhaps abandoned completely even in combination.[52] Second-line treatments are combinations of benzodiazepines and antipsychotics and third line would probably now be intravenous benzodiazepines and then ketamine (2–5mg/kg IM), assuming intubation facilities are available.

Practical measures

Plans for the management of individual patients should ideally be made in advance. The aim is to prevent disturbed behaviour and reduce risk of violence. Nursing interventions (de-escalation, time out, seclusion[53]), increased nursing levels, transfer of the patient to a psychiatric intensive care unit (PICU) and pharmacological management are options that may be employed. Care should be taken to avoid combinations and high cumulative doses of antipsychotic drugs. The monitoring of routine physical observations after RT is essential. Note that RT is often viewed as punitive by patients. There is little research into the patient experience of RT.

The aims of RT are threefold:

- To reduce suffering for the patient: psychological or physical (through self-harm or accidents).
- To reduce risk of harm to others by maintaining a safe environment.
- To do no harm (by prescribing safe regimes and monitoring physical health).

Note: Despite the need for rapid and effective treatment, concomitant use of two or more antipsychotics (antipsychotic polypharmacy) should be avoided on the basis of risk associated with QT prolongation (common to almost all antipsychotics). This is a particularly important consideration in RT where the patient's physical state predisposes to cardiac arrhythmia.

Zuclopenthixol acetate

Zuclopenthixol acetate (ZA) is widely used in the UK and elsewhere in Europe and is best known by its trade name Acuphase. Zuclopenthixol itself is a thioxanthene dopamine antagonist first introduced in the early 1960s. ZA is not a rapidly tranquillising agent. Its elimination half-life is around 20 hours. Intramuscular injection of zuclopenthixol base results in rapid absorption and a duration of action of 12–24 hours. By slowing absorption after IM injection, the biological half-life (and so duration of action) becomes dependent on the rate of release from the IM reservoir. This can be achieved by esterification of the zuclopenthixol molecule; the rate of release being broadly proportion to the length of the ester carbon chain. Thus, zuclopenthixol decanoate is slow to act but very long-acting as a result of retarded release after IM injection. Zuclopenthixol acetate (with eight carbon atoms fewer) would be expected to provide relatively prompt release but with an intermediate duration of action. The intention of the manufacturers was that the use of ZA would obviate the need for repeated IM injections in disturbed patients.

An initial pharmacokinetic study of ZA included 19 patients 'in whom calming effect by parenteral neuroleptic was considered necessary'.[54] Zuclopenthixol was detectable in the plasma after 1–2 hours but did not reach peak concentrations until around 36 hours after dosing. At 72 hours, plasma levels were around a third of those at 36 hours. The clinical effect of ZA was not rapid – 10 of 17 patients exhibited minimal or no change in psychotic symptoms at 4 hours. Sedation was evident at 4 hours, but it had effectively abated by 72 hours.

A follow-up study by the same research group[55] examined more closely the clinical effects of ZA in 83 patients. The authors concluded that ZA produced 'pronounced and rapid reduction in psychotic symptoms'. In fact, psychotic symptoms were first assessed only after 24 hours and so a claim of rapid effect is not reasonably supported. Sedative effects were measured after two hours when a statistically significant effect was observed – at baseline mean sedation score was 0.0 (0 = no sign of sedation) and at 2 hours 0.6 (1 = slightly sedated). Maximum sedation was observed at 8 hours (mean score 2.2; 2 = moderately sedated). At 72 hours mean score was 1.1. Dystonia and rigidity were the most commonly reported adverse effects.

Two independently conducted open studies, produced similar results – a slow onset of effect peaking at 24 hours and still being evident at 72 hours.[56,57] The first UK study was reported in 1990.[58] In the trial, a significant reduction in psychosis score was first evident at 8 hours and scores continued to fall until the last measurement at 72 hours. Of 25 patients assessed only 4 showed signs of tranquillisation at 1 hour (19 at 2 hours and 22 at 24 hours).

A comparative trial of ZA[59] examined its effects and those of IM/oral haloperidol and IM/oral zuclopenthixol base (in multiple doses over 6 days). The two non-ester, IM/oral preparations produced a greater degree of sedation at 2 hours than did ZA, but the effect of ZA and zuclopenthixol was more sustained than with haloperidol over 144 hours (although patients received more zuclopenthixol doses). No clear differences between treatments were detected, with the exception of the slow onset of effect of ZA. The number of doses given varied substantially: ZA 1–4; haloperidol 1–26 and zuclopenthixol 1–22. This is the key (and perhaps unique) advantage of ZA – it reduces the

need for repeat doses in acute psychosis. Indeed this was the principal finding of the first double-blind study of ZA.[60] Participants were given either ZA or haloperidol IM and assessed over three days. Changes in BPRS and CGI scores were near identical on each daily assessment. However, only 1 of 23 ZA patients required a second injection, whereas 7 of 21 required a repeat dose of haloperidol. Speed of onset was not examined. Similar findings were reported by Thai researchers comparing the same treatments,[61] and in three other studies of moderate size (n = 44,[62] n = 40,[63] n = 50).[64] In each study, the timing of assessments was such that time to onset of effect could not be determined.

A Cochrane review[65] included all of the above comparative studies as well as three further studies[66–68] for which we were unable to obtain full details. The Cochrane authors concluded that all studies were methodically flawed and poorly reported and that ZA did not appear to have a 'rapid onset of action'. They noted that ZA was probably no less effective than other treatments and that its use might 'result in less numerous coercive injections'.

Overall, the utility of ZA in rapid tranquillisation is limited by a somewhat delayed onset of both sedative and antipsychotic actions. Sedation may be apparent in a minority of patients after 2–4 hours, but antipsychotic action is evident only after 8 hours. If ZA is given to a restrained patient, their behaviour on release from restraint is likely to be unchanged and will remain as such for several hours. ZA has a role in reducing the number of restraints for IM injection, but it has no role in rapid tranquillisation.

Guidelines for the use of zuclopenthixol acetate (Acuphase)

Zuclopenthixol acetate (ZA) is not a rapidly tranquillising agent. It should be used only after an acutely psychotic patient has required *repeated* injections of short-acting antipsychotic drugs such as haloperidol or olanzapine, or sedative drugs such as lorazepam. It is perhaps best reserved for those few patients who have a prior history of good response to Acuphase.

ZA should be given only when enough time has elapsed to assess the full response to previously injected drugs: allow 15 minutes after IV injections; 60 minutes after IM.

ZA should never be administered for rapid tranquillisation (onset of effect is too slow) or to a patient who is physically resistant (risk of intravasation and oil embolus) or to neuroleptic-naïve patients (risk of prolonged EPSE).

Rapid tranquillisation summary

In an emergency situation – *Assess if there may be a medical cause.*[69] *Optimise regular prescription. The aim of pharmacological treatment is to calm the patient but not to oversedate. Note: lower doses should be used for children, adolescents and older adults. Patients' levels of consciousness and physical health should be monitored after administration of parenteral medication (see protocol)*

Step Intervention

1 De-escalation, time out, placement, etc., as appropriate

2 Offer oral treatment

If patient is prescribed a regular antipsychotic:
Lorazepam 1–2mg
Promethazine 25–50mg

Monotherapy with **buccal midazolam** may avoid the need for IM treatment. Dose: 10mg
Note that this preparation is unlicensed

If patient is not already taking a regular oral or depot antipsychotic:

- **Olanzapine** 10mg or
- **Risperidone** 1–2mg or
- **Quetiapine** 50–100mg or
- **Haloperidol** 5mg (best with promethazine 25mg). Note that the EU SPC for haloperidol recommends: A pre-treatment ECG and to avoid concomitant antipsychotics
- **Inhaled loxapine** 10mg Note that use of this preparation requires the co-operation of the patient, and that bronchospasm is a rare side effect (have a salbutamol inhaler to hand).

Repeat after 45–60 minutes, if necessary. Consider combining sedative and antipsychotic treatment.
Go to step 3 if two doses fail or sooner if the patient is placing themselves or others at significant risk.

3 Consider IM treatment

Lorazepam 2mg[ab]	Have flumazenil to hand in case of benzodiazepine-induced respiratory depression.
Promethazine 50mg[c]	IM promethazine is a useful option in a benzodiazepine-tolerant patient.
Olanzapine 10mg[d]	IM olanzapine should NOT be combined with an IM benzodiazepine, particularly if alcohol has been consumed.[70]
Aripiprazole 9.75mg	Less hypotension than olanzapine, but less effective[5,13,71]
Haloperidol 5mg	**Haloperidol should be the last drug considered** ■ The incidence of acute dystonia is high; combine with IM promethazine and ensure IM procyclidine is available ■ Pre-treatment ECG required

Repeat after 30–60 minutes if insufficient effect. Combinations of haloperidol and lorazepam or haloperidol and promethazine may be considered if single drug treatment fails. Drugs must not be mixed in the same syringe. IM olanzapine must never be combined with IM benzodiazepine.

4 Consider **IV treatment**

- **Diazepam** 10mg over at least 2 minutes[be]
- Repeat after 5–10 minutes if insufficient effect (up to 3 times)
- Have flumazenil to hand

5 Seek expert advice[f]
Consider transfer to medical unit for administration of **IM ketamine**

Notes
a. Carefully check administration and dilution instructions, which differ between manufacturers. Many centres use 4mg. An alternative is IM midazolam 5–15mg. 5mg is usually sufficient. The risk of respiratory depression is dose-related with both drugs but generally greater with midazolam.
b. Caution in the very young and elderly and those with pre-existing brain damage or impulse control problems, as disinhibition reactions are more likely.[72]

(*Continued*)

Rapid tranquillisation summary (*Continued*)

c. Promethazine has a slow onset of action but is often an effective sedative. Dilution is not required before IM injection. May be repeated up to a maximum of 100mg/day. Wait 1–2 hours after injection to assess response. Note that promethazine alone has been reported, albeit very rarely, to cause NMS,[73] although it is an extremely weak dopamine antagonist. Note also the potential pharmacokinetic interaction between promethazine and haloperidol (reduced metabolism of haloperidol), which may confer risk if repeated doses of both are administered.

d. Recommended by NICE only for moderate behavioural disturbance, but data from a large observational study also supports efficacy in clinical emergencies.

e. Use Diazemuls to avoid injection site reactions. Lorazepam can also be given IV. IV therapy may be used instead of IM when a very rapid effect is required. IV therapy also ensures near-immediate delivery of the drug to its site of action and effectively avoids the danger of inadvertent accumulation of slowly absorbed IM doses. IV doses can be repeated after only 5–10 minutes if no effect is observed. Midazolam can also be used IV, but respiratory depression is common.[1]

f. Options at this point are limited, although the wider use of IM ketamine has improved the range of options available. IM amylobarbitone and IM paraldehyde have been used in the past but are used now only extremely rarely and are generally not easy to obtain. IV olanzapine, IV droperidol and IV haloperidol are possible but adverse effects are fairly common. ECT is also an option.

Rapid tranquillisation – physical monitoring

After any parenteral drug administration, monitor as follows:

- **Temperature**
- **Pulse**
- **Blood pressure**
- **Respiratory rate**

Every 15 minutes for 1 hour, and then hourly until the patient is ambulatory. Patients who refuse to have their vital signs monitored or who remain too behaviourally disturbed to be approached should be observed for signs/symptoms of pyrexia, hypoxia, hypotension, over-sedation and general physical well-being.

If the patient is asleep or **unconscious**, the continuous use of pulse oximetry to measure oxygen saturation is desirable. A nurse should remain with the patient until ambulatory.

ECG and haematological monitoring are also strongly recommended when parenteral antipsychotics are given, especially when higher doses are used.[74,75] Hypokalaemia, stress and agitation place the patient at risk of cardiac arrhythmia[76] (see the section on 'QT prolongation'). ECG monitoring is formally recommended for all patients who receive haloperidol.

Remedial measures in rapid tranquillisation

Problem	*Remedial measures*
Acute dystonia (including oculogyric crises)	Give **procyclidine** 5–10mg IM or IV
Reduced respiratory rate (<10/min) or oxygen saturation (<90%)	Give oxygen, raise legs, ensure patient is not lying face down. Give **flumazenil** if benzodiazepine-induced respiratory depression suspected (see protocol) If induced by any other sedative agent: **transfer to a medical bed and ventilate mechanically.**

(*Continued*)

Remedial measures in rapid tranquillisation (*Continued*)	
Irregular or slow (<50/min) **pulse**	**Refer** to specialist medical care immediately.
Fall in blood pressure (>30mmHg orthostatic drop or < 50mmHg diastolic)	**Have patient lie flat**, tilt bed towards head. Monitor closely.
Increased temperature	(risk of NMS and perhaps arrhythmia). Check creatine kinase urgently.

Guidelines for the use of flumazenil	
Indication for use	If, after the administration of lorazepam, midazolam or diazepam, respiratory rate falls below 10/min.
Contraindications	Patients with epilepsy who have been receiving long-term benzodiazepines.
Caution	Dose should be carefully titrated in hepatic impairment.
Dose and route of administration	***Initial*:** 200µg ***intravenously*** over 15 seconds – if required level of consciousness not achieved after 60 seconds, then, ***Subsequent dose:*** 100µg over 15 seconds.
Time before dose can be repeated	60 seconds.
Maximum dose	1mg in 24 hours (one initial dose and eight subsequent doses).
Side-effects	Patients may become agitated, anxious or fearful on awakening. Seizures may occur in regular benzodiazepine users.
Management	Side-effects usually subside.
Monitoring	
■ **What to monitor?**	Respiratory rate
■ **How often?**	Continuously until respiratory rate returns tobaseline level. Flumazenil has a short half-life (much shorter than diazepam) and respiratory function may recover and then deteriorate again.

***Note: If respiratory rate does not return to normal or patient is not alert after initial doses given, assume that* sedation is due to some other cause.**

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Antipsychotic depots/long-acting injections (LAIs)

Long-acting injectable (LAI) preparations of antipsychotic medication are commonly prescribed in clinical practice, especially in the UK, Australasia and the EU. Observational studies have confirmed that continued treatment is associated with fewer relapses and rehospitalisations compared with oral antipsychotic treatment,[1–5] although there are confounding factors in such studies, such as indication bias.

A Cochrane systematic review of randomised trials comparing maintenance treatment with antipsychotic medication and placebo for people with schizophrenia found LAI antipsychotic medications (in particular, LAI haloperidol and fluphenazine) were more effective than oral antipsychotic medications.[6] However, the authors noted that only head-to-head comparisons of oral and LAI antipsychotic treatment can determine whether the latter are more effective. The findings of such RCTs have generally failed to show a clear superiority for LAI antipsychotic medications,[7–9] although this may be partly related to study design and methodology issues.[2] Specifically, double-blind RCTs are generally relatively short term, and the study samples will tend to be biased towards patients with rather less severe illness, fewer comorbid conditions and better adherence to medication.[10,11] RCTs conducted in a more naturalistic manner may better show the advantages of depots.[12] However, all studies of all types clearly demonstrate that continuous treatment with depots does not confer complete protection against relapse.[13]

LAI antipsychotic medication is recommended where a patient has expressed a preference for such a formulation because of its convenience or where avoidance of covert non-adherence is considered a clinical priority.[14,15] While LAI medication does not ensure adherence, it does assure awareness of adherence, unlike the use of oral medication. Thus, failure to adhere, which may be a sign of relapse or a potential cause, will be signalled by delayed attendance for, or refusal of, an injection, allowing the clinical team to intervene promptly. Another possible advantage for LAI antipsychotic medication is that its use may help clarify whether an unsatisfactory therapeutic response to antipsychotic medication is due to adherence problems or a refractory illness. Many apparently refractory patients are simply non-adherent to oral medication, sometimes completely so.[16] Furthermore, an LAI antipsychotic regimen provides the opportunity for regular scrutiny of a patient's mental state and side effects by the health care professional administering the injection.[17]

The proportion of patients with schizophrenia prescribed LAI antipsychotic medications varies between and across countries suggesting that the use of such medication is influenced by factors beyond the extent of poor adherence. Greater understanding of these factors might allow us to identify possible barriers to the optimal implementation of this treatment.[18–20] A US study found that American first-episode patients were largely willing to accept long-acting treatment.[21] This suggests that low usage of depots in the USA might be largely a result of reluctance on the part of clinicians, rather than patients.

Advice on prescribing LAIs

- **For LAI FGAs, give a test dose**
  Because of its long half-life, any adverse effects that result from the administration of an LAI antipsychotic medication are likely to be long-lived. Therefore, such treatment

should be avoided in patients with a history of serious adverse effects that would warrant immediate discontinuation of the medication, such as neuroleptic malignant syndrome (NMS). For LAI FGAs, a test dose consisting of a small dose of active drug in a small volume of oil serves a dual purpose – it is a test of the patient's sensitivity to EPS and of any sensitivity to the base oil. For LAI SGAs, test doses may not be required (there is a lower propensity to cause EPS and the aqueous base not known to be allergenic), although they could be considered appropriate where a patient is suspected of being non-adherent to oral antipsychotic medication and the LAI preparation will be the first exposure to guaranteed antipsychotic medication delivery. For both LAI FGAs and SGAs, prior treatment with the equivalent oral formulation is preferred to assess efficacy and tolerability, but it is not always necessary from a pharmacokinetic viewpoint. Most SGA depots can be used as sole treatment from the outset, although loading doses are usually necessary (e.g. for paliperidone and aripiprazole).

- **Begin with the lowest therapeutic dose**
  There are few data showing clear dose–response effects for FGA LAI antipsychotic medication. There is some information indicating that low doses (within the licensed range) may be at least as effective as higher ones,[22–25] but whether the dosages and frequency of injections for LAI antipsychotic medications achieve the optimal benefit–risk balance seems uncertain.[26–28]
- **Administer at the longest possible licensed interval**
  All LAI antipsychotic medications can be safely administered at their licensed dosing intervals, bearing in mind the maximum recommended single dose. There is no evidence to suggest that shortening the dose interval improves efficacy. Moreover, the intramuscular injection site can be a cause of discomfort and pain, so less frequent administration is desirable. Although some patients are reported to deteriorate in the days before their next injection is due, plasma drug concentrations may continue to fall, albeit slowly, for some hours (or even days with some preparations) after each injection. In this context, a patient's apparent recovery soon after the injection is given makes no sense. More importantly, at steady state, trough plasma levels (immediately pre- and post-dose) are usually substantially above the threshold concentration required for therapeutic effect.
- **Adjust doses only after an adequate period of assessment**
  Attainment of peak plasma levels, therapeutic effect and steady-state plasma levels are all delayed with LAI antipsychotic medications, compared with oral medications. Doses may be *reduced* if adverse effects occur but should only be increased after careful assessment over at least one month, and preferably longer. Note that with most LAI antipsychotic preparations, at the start of treatment, plasma drug levels increase over several weeks to months without any increase in the dosage. This is due to accumulation: steady state is only achieved after at least 6–8 weeks. Dose increases during this initial period are therefore illogical and impossible to evaluate properly. With continued LAI antipsychotic treatment, the monitoring and recording of therapeutic efficacy, side effects and any impact on physical health are recommended
- **LAIs are not recommended for those who are antipsychotic-naïve**
  Tolerability to some LAI antipsychotic medications can be established by using the oral form of the same drug for two weeks before starting. Good examples here are haloperidol, aripiprazole and paliperidone (using oral risperidone).

Table 1.4 Antipsychotic long-acting injections – doses and frequencies[15]

Drug	UK Trade Name	Licences injection site	Test dose (mg)	Dose range (mg/week)	Dosing interval (weeks)	Comments
Aripiprazole	(Abilify Maintena)	Buttock	Not required**	300–400mg monthly	Monthly	Does not increase prolactin; oral loading required
Flupentixol decanoate	(Depixol)	Buttock or thigh	20	50mg every 4 weeks to 400mg a week	2–4	Maximum licensed dose is high relative to other LAIs
Fluphenazine decanoate	(Modecate)	Gluteal region	12.5	12.5mg every 2 weeks to 100mg every 2 weeks	2–5	High EPS
Haloperidol decanoate	(Haldol)	Gluteal region	25*	50–300mg every 4 weeks	4	High EPS
Olanzapine pamoate	(ZypAdhera)	Gluteal	Not required**	150mg every 4 weeks to 300mg every 2 weeks	2–4	Risk of post-injection syndrome
Paliperidone palmitate (monthly)	(Xeplion)	Deltoid or gluteal	Not required**	50–150mg monthly	Monthly	Loading dose required at treatment initiation
Paliperidone palmitate (3-monthly)	(Trevicta)	Deltoid or gluteal	Not required***	175–525mg every 3 months	3 months	
Pipothiazine palmitate	(Piportil)	Gluteal region	25	50–200mg every 4 weeks	4	? Lower incidence of EPS (relative to other FGAs)
Risperidone microspheres	(Risperdal Consta)	Deltoid or gluteal	Not required**	25–50mg every 2 weeks	2	Drug release delayed for 2–3 weeks – oral therapy required
Zuclopenthixol decanote	(Clopixol)	Buttock or thigh	100	200mg every 3 weeks to 600mg a week	2–4	? Slightly better efficacy than LAI FGAs

Notes:

- The doses mentioned above are for adults. Check formal labelling for appropriate doses in the elderly.
- After a test dose, wait 4–10 days then titrate to maintenance dose according to response (see product information for individual drugs).
- Avoid using shorter dose intervals than those recommended except in exceptional circumstances (e.g. long interval necessitates high volume (>3–4ml?) injection). Maximum licensed single dose overrides longer intervals and lower volumes. For example, zuclopenthixol 500mg every week is licensed, whereas 1,000mg every two weeks is not (more than the licensed maximum of 600mg is administered). Always check official manufacturer's information.

*Test dose not stated by manufacturer.

**Tolerability and response to the oral preparation should be established before administering the LAI. With respect to paliperidone LAI, oral risperidone can be used for this purpose.

***May not be started until the completion of 4 months' treatment with monthly LAI.

- **Adding an oral antipsychotic medication risks a high-dose prescription**
  The regular prescription of an oral antipsychotic medication in addition to an LAI antipsychotic preparation was once common with FGAs.[17,29] While this may be a possible strategy for the control of breakthrough symptoms and offer greater flexibility in dosage titration, the safety and tolerability of such a combination is uncertain, particularly over the longer term.[30] The co-prescription of an LAI and oral antipsychotic medication may well result in a, possibly inadvertent, high-dose prescription, with an increased side-effect burden and implications for physical health monitoring.[10,17]

Differences between LAIs

None of the individual LAI FGAs has emerged as clearly superior in efficacy, although there is some suggestion of an advantage for zuclopenthixol decanoate in terms of time to discontinuation and hospitalisation, but perhaps at the expense of a greater side-effect burden.[31–33] Cochrane reviews have been completed for pipotiazine palmitate,[34] flupentixol decanoate,[35] zuclopenthixol decanoate,[36] haloperidol decanoate[37] and fluphenazine decanoate.[38]

The LAI SGAs, aripiprazole, paliperidone, risperidone and olanzapine, also have comparable efficacy but vary in their liability for particular adverse effects, such as weight gain, metabolic effects, EPS, and raised plasma prolactin.[39–42] For example, LAI paliperidone is associated with substantial increases in serum prolactin,[41] and LAI olanzapine can cause significant weight gain and is associated with a post-injection delirium/sedation syndrome, assumed to be caused by unintended partial intravascular injection or blood vessel injury.[43,44] Because of the nature of the pharmacokinetic profile of LAI risperidone, administration of an oral antipsychotic medication is required in the three weeks after the first injection (Table 1.4).[45,46] Details on dosing of individual SGAs are given elsewhere in this chapter.

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Depot/LAI antipsychotics – pharmacokinetics

Drug	UK Trade Name	Time to peak (days)*	Plasma half-life (days)	Time to steady state (weeks)**
Aripiprazole[1]	(Abilify Maintena)	7d	30–46d	~20W
Aripiprazole lauroxil[2–4]	(Aristada (in USA))	44–50d	~54–57d	~16W
Aripiprazole lauroxil nanocrystal[4–6]****	(Aristada Initio (in USA))	4d	~15–18d	
Flupentixol decanoate[7,8]	(Depixol)	4–7d	8–17d	~8–12W
Fluphenazine decanoate[4,9–11]	(Modecate)	8–12d***	7–10d	~8W
Haloperidol decanoate[12,13]	(Haldol)	7d	21d	~14W
Olanzapine pamoate[4,14,15]	(ZypAdhera)	2–3d	30d	~12W
Paliperidone palmitate[4,16] (monthly)	(Xeplion)	13d	25–49d	~20W
Paliperidone palmitate[17,18] (three monthly)	(Trevicta)	25d	Deltoid: 84–95d Gluteal: 118–139d	~52W
Pipotiazine palmitate[19,20]	(Piportil)	7–14d	15d	~9W
RBP-7000[4,21] (risperidone sc monthly)	(Perseris (in USA))	1st peak ~1d 2nd peak ~11d	~8–9d	~8W
Risperidone microspheres[22,23]	(Risperidal Consta)	~30d	4d	~8W
Zuclopenthixol decanoate[7,19,24]	(Clopixol)	4–7d	19d	~12W

*Time to peak is not the same as time to reach therapeutic plasma concentration, but both are dependent on dose. For large (loading) doses, therapeutic activity is often seen before attaining peak levels. For low (test) doses, the initial peak level may be sub-therapeutic.
**Attainment of steady state (SS) follows logarithmic, not linear characteristics: around 90% of SS levels are achieved in three half-lives. Time to attain steady state is independent of dose and dosing frequency (i.e. you can't hurry it up by giving more, more often). Loading doses can be used to produce prompt therapeutic plasma levels but time to SS remains the same.
***Some estimates suggest peak concentrations after only a few hours.[24,25] It is likely that fluphenazine decanoate produces two peaks – one on the day of injection and a second slightly higher peak a week or so later.[12]
****used to initiate treatment with Aristada, IM injection with one 30 mg oral dose of aripiprazole; not designed for repeat dosing.

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Management of patients on long-term depots/LAIs

All patients receiving long-term treatment with antipsychotic medication should be seen by their responsible psychiatrist at least once a year (ideally more frequently) in order to review their treatment and progress. A systematic assessment of tolerability and safety should constitute part of this review. The assessment of adverse effects should include EPS (principally parkinsonism, akathisia, and tardive dyskinesia). Assessment of tardive dyskinesia can be recorded by scoring the Abnormal Involuntary Movement Scale (AIMS).[1,2] While some study findings have suggested that LAI antipsychotic medication may be more likely to be associated with tardive dyskinesia than oral antipsychotic medication, this remains uncertain:[3–5] when using the same antipsychotic medication, the risk of tardive dyskinesia does not appear to be different between the LAI and oral formulations.[6,7]

For most people with multi-episode schizophrenia, long-term antipsychotic treatment, even lifelong treatment, may be necessary. Overall, for those with stable illnesses, it has been proposed that the dosage of continuing antipsychotic treatment should be at least 50% of the standard daily dosage, as reduction below this level is associated with a greater risk of relapse.[8] Thus, long-term follow-up is essential when antipsychotic dosage is decreased, particularly to very low doses, as such reduction is associated with a greater risk of treatment failure, hospitalisation and relapse,[9] which may only become evident over the longer term.

However, with the long-term treatment of patients with stable illness with LAI antipsychotic formulations, dose reduction may be considered on the basis that patients often receive supratherapeutic doses. In trials, haloperidol decanoate is optimally effective at 75mg every four weeks,[9,10] paliperidone palmitate at 50mg a month.[11] Doses as low as these are almost unheard of in practice. Furthermore, the threshold level of striatal dopamine D2 receptor occupancy required for relapse prevention may be lower than that for the treatment of an acute episode.[12–14] Nevertheless, for people with schizophrenia, reduction below the standard dosage seems to be clearly associated with a greater risk of relapse, particularly in the longer term. A study comparing fluphenazine decanoate at a low (5mg every two weeks) or standard (25mg every two weeks) dosage found no difference in outcome at one year but a substantial disadvantage for the lower dose at two years (relapse in 69% and 36%, respectively).[15] However, in the same study, the facility to increase the dose when symptoms emerged removed the advantage for the higher dose. Another trial comparing low-dose fluphenazine decanoate (1.25–5mg every two weeks) with standard dosage (12.5 to 50mg every 2 weeks) also found the low-dose to be clearly inferior, with cumulative one-year relapse rates of 56% and 7%, respectively.[16] Similarly, an RCT comparison of four, fixed, monthly doses (25mg, 50mg, 100mg or 200mg) of LAI haloperidol medication over a year[17] found that the standard 200mg dose was associated with the lowest rate of relapse and symptomatic exacerbation (15%), compared with the 100mg (23%) or 50mg (25%) doses (although not statistically significant), but only a minimally increased risk of adverse effects.

There is no simple formula for deciding when or whether to reduce the dose of continuing antipsychotic treatment, and so a risk/benefit analysis must be carried out for every patient. Many patients, it should be noted, prefer to receive LAI antipsychotic preparations.[7,18]

When considering dose reduction, the following prompts may be helpful:

- Is the patient symptom-free and if so for how long? Long-standing, non-distressing symptoms which have not previously been responsive to medication may be excluded.
- How severe, tolerable and disabling are the side effects (EPS including tardive dyskinesia, metabolic side effects including obesity, etc.)? When patients report no or minimal adverse effects, it is usually sensible to continue treatment and monitor closely for signs of tardive dyskinesia.
- What is the previous pattern of illness? Consider the speed of onset, duration and severity of past relapses and any dangers or risks posed to self or others
- Has dosage reduction been attempted before? If so, what was the outcome?
- What are the patient's current social circumstances? Is it a period of relative stability, or should stressful life events be anticipated?
- What is the potential social cost of relapse (e.g. is the patient the sole breadwinner for a family)?
- Is the patient able to monitor his/her own symptoms? If so, will he/she seek appropriate help?

If, after consideration of the above, the decision is taken to reduce the medication dose, the patient's family should be involved and a clear explanation given of what should be done if and when symptoms return or worsen. It would then be reasonable to proceed in the following manner:

- If it has not already been done, any co-prescribed oral antipsychotic medication should be discontinued.
- Where the product labelling allows, the interval between injections should be increased to up to 4 weeks before decreasing the dose given each time.
- The dose should be reduced by no more than a third at any one time. Note: special considerations apply to risperidone Consta LAI.
- Decrements should, if possible, be made no more frequently than every 3 months, preferably every 6 months or more. The slower the rate of withdrawal, the longer the time to relapse.[19]
- Discontinuation of medication should not be seen as the ultimate aim of the above process, although it sometimes results. While an intermittent, targeted (symptom-triggered) treatment approach with antipsychotic medication is not as effective as continuous treatment, it may be preferable to no treatment.[20–22]

If the patient becomes symptomatic, this should be seen not as a failure but rather as an important step in determining the minimum effective dose that the patient requires.

For more discussion, see the section on long-term antipsychotic treatment in this chapter.

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Aripiprazole long-acting injection

Abilify brands

Aripiprazole lacks the prolactin-related and metabolic adverse effects of other SGA LAIs and so is a useful alternative to them. Placebo-controlled studies show a good acute and longer term effect in the treatment of schizophrenia.[1] The FDA has also approved Aripiprazole LAI for maintenance monotherapy treatment of bipolar I disorder in adults.[2] Oral aripiprazole 10mg/day for 14 days is recommended initially to establish tolerability and response. One of two regimens may be followed for administering the starting dose of aripiprazole LAI.[3]

One-injection start

On the day of initiation, administer one injection of 400mg aripiprazole LAI and continue treatment with 10mg to 20mg oral aripiprazole per day for 14 consecutive days (28 days in total) to maintain therapeutic aripiprazole concentrations during initiation.

Or

Two-injection start

On the day of initiation, administer two separate injections of 400mg aripiprazole LAI at separate injection sites in two different muscles (separate gluteal, separate deltoid or gluteal and deltoid injection sites) along with one 20mg dose of oral aripiprazole. Oral therapy should not continue after this point.

One month after the day of initiation, begin a regimen of 400mg each month.

After the one-injection + oral starting regimen, peak plasma levels are seen 7 days after the injection and trough levels at four weeks.[4] At steady state, peak plasma levels are up to 50% higher than the first dose peak and trough plasma levels only slightly below the first dose peak.[4] Dose adjustments should take this into account. A population pharmacokinetic modelling study indicated that the two-injection start regimen would produce comparable aripiprazole plasma concentrations to the one injection start method.[5]

A lower dose of 300mg a month can be used in those not tolerating 400mg. A dose of 200mg a month may only be used for those patients receiving particular enzyme inhibiting drugs. The incidence of akathisia, insomnia, nausea and restlessness is similar to that seen with oral aripiprazole[6,7]

There are no formal recommendations for switching to aripiprazole, but we present next recommendations based on our interpretation of available pharmacokinetic data.