The Maudsley®

Prescribing Guidelines in Psychiatry

14TH EDITION

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

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The Maudsley® Prescribing Guidelines in Psychiatry

The Maudsley Guidelines

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The Maudsley[®] Prescribing Guidelines in Psychiatry

14th Edition

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Contents

	Preface	xi
	Acknowledgments	xii
	Notes on using The Maudsley® Prescribing Guidelines in Psychiatry	xiii
	List of abbreviations	XV
Part 1	Drug treatment of major psychiatric conditions	1
Chapter 1	Schizophrenia and related psychoses	3
	ANTIPSYCHOTIC DRUGS	3
	General introduction	3
	General principles of prescribing	8
	Minimum effective doses	9
	Licensed maximum doses	12
	Equivalent doses	14
	High-dose antipsychotics: prescribing and monitoring	16
	Combined antipsychotics (antipsychotic polypharmacy)	20
	Antipsychotic prophylaxis	25
	Negative symptoms	32
	Monitoring	38
	Relative adverse effects – a rough guide	41
	Treatment algorithms for schizophrenia	42
	First-generation antipsychotics - place in therapy	46
	NICE guidelines for the treatment of schizophrenia	48
	Antipsychotic response - to increase the dose, to switch, to add or	
	just wait – what is the right move?	51
	Acutely disturbed or violent behaviour	56
	Antipsychotic depots/long-acting injections (LAIs)	67
	Depot/LAI antipsychotics – pharmacokinetics	72
	Management of patients on long-term depots/LAIs	74
	Aripiprazole long-acting injection	77
	Olanzapine long-acting injection	80
	Paliperidone palmitate long-acting injection	83
	Risperidone long-acting injection	87
	Risperidone subcutaneous long-acting injection	91

	Newer long-acting injectable antipsychotic preparations	92
	Penfluridol weekly	95
	Electroconvulsive therapy and psychosis	96
	Omega-3 fatty acid (fish oils) in schizophrenia	99
	Stopping antipsychotics	102
	ANTIPSYCHOTIC ADVERSE EFFECTS	109
	Extrapyramidal symptoms	109
	Akathisia	114
	Treatment of tardive dyskinesia	117
	Antipsychotic-induced weight gain	123
	Treatment of antipsychotic-induced weight gain	125
	Neuroleptic malignant syndrome	131
	Catatonia	135
	ECG changes – QT prolongation	141
	Effect of antipsychotic medications on plasma lipids	149
	Diabetes and impaired glucose tolerance	153
	Blood pressure changes with antipsychotics	160
	Hyponatraemia in psychosis	164
	Hyperprolactinaemia	168
	Sexual dysfunction	172
	Pneumonia	181
	Switching antipsychotics	183
	Venous thromboembolism	187
	REFRACTORY SCHIZOPHRENIA AND CLOZAPINE	190
	Clozapine initiation schedule	190
	Intramuscular clozapine	192
	Optimising clozapine treatment	193
	Alternatives to clozapine	198
	Re-starting clozapine after a break in treatment	207
	Guidelines for the initiation of clozapine for patients based in the community	
	CLOZAPINE ADVERSE EFFECTS	212
	Clozapine: common adverse effects	212
	Clozapine: uncommon or unusual adverse effects	217
	Clozapine: serious haematological and cardiovascular adverse effects	222
	Clozapine-induced hypersalivation	227
	Clozapine-induced gastrointestinal hypomotility (CIGH)	232
	Clozapine, neutropenia and lithium	236
	Clozapine and chemotherapy	242
	Clozapine-genetic testing for clozapine treatment	244
Chapter2	Bipolar disorder	247
	Lithium	247
	Valproate	257
	Carbamazepine	264
	Antipsychotics in bipolar disorder	269
	Antipsychotic long-acting injections in bipolar disorder	274
	Physical monitoring for people with bipolar disorder	277
	Treatment of acute mania or hypomania	279
	Rapid cycling bipolar affective disorder	285

	Bipolar depression	288
	Prophylaxis in bipolar disorder	296
	Stopping lithium and mood stabilisers	301
Chapter 3	Depression and anxiety disorders	305
	Introduction to Depression	305
	Official guidance on the treatment of depression	305
	Antidepressants – general overview	307
	Recognised minimum effective doses of antidepressants	312
	Drug treatment of depression	314
	Management of treatment-resistant depression – first choice	317
	Management of treatment-resistant depression – second choice	321
	Treatment-resistant depression – other reported treatments	323
	Ketamine	328
	Psychotic depression	332
	Switching antidepressants	336
	Antidepressant withdrawal symptoms	343
	Stopping antidepressants	348
	Electroconvulsive therapy (ECT) and psychotropic drugs	353 357
	Psychostimulants in depression	362
	Post-stroke depression Antidepressants – alternative routes of administration	366
	Antidepressants – anemative routes of administration	374
	Drug interactions with antidepressants	374
	Cardiac effects of antidepressants – summary	383
	Antidepressant-induced arrhythmia	389
	Antidepressant-induced armytimma Antidepressant-induced hyponatraemia	393
	Antidepressants and hyperprolactinaemia	398
	Antidepressants and diabetes mellitus	401
	Antidepressants and sexual dysfunction	404
	SSRIs and bleeding	409
	St. John's Wort	417
	Antidepressants: relative adverse effects – a rough guide	421
	Anxiety spectrum disorders	423
	Benzodiazepines in the treatment of psychiatric disorders	436
	Benzodiazepines, z-drugs and gabapentinoids: dependence, detoxification	4.40
	and discontinuation	440
	Benzodiazepines and disinhibition	448
Chapter 4	Addictions and substance misuse	451
	Introduction	451
	Alcohol dependence	453
	Alcohol withdrawal delirium – delirium tremens	472
	Opioid dependence	474 503
	Nicotine and smoking cessation Pharmacological treatment of dependence on stimulants	503
	GHB and GBL dependence	511
	Benzodiazepine misuse	514
	Synthetic cannabinoid receptor agonists (SCRAs)	520
	synthetic cannabiliou receptor agoinsts (SOLLIS)	520

	Drug-induced acute behavioural disturbance (ABD) in acute admissions	524
	Interactions between 'street drugs' and prescribed psychotropic drugs	526
	Drugs of misuse – a summary	530
	Substance misuse in pregnancy	535
Part 2	Drug treatment of special patient groups	537
Chapter 5	Children and adolescents	539
	Principles of prescribing practice in childhood and adolescence	539
	Depression in children and adolescents	541
	Bipolar illness in children and adolescents	547
	Psychosis in children and adolescents	554
	Anxiety disorders in children and adolescents	556
	Obsessive compulsive disorder (OCD) and body dysmorphic disorder (BDD)	5(1
	in children and adolescents Post-traumatic stress disorder in children and adolescents	561
	Attention deficit hyperactivity disorder	567 569
	Autism Spectrum Disorder	578
	Tics and Tourette syndrome	587
	Melatonin in the treatment of insomnia in children and adolescents	593
	Rapid tranquillisation (RT) in children and adolescents	596
	Doses of commonly used psychotropic drugs in children and adolescents	599
Chapter 6	Prescribing in older people	601
	General principles	601
	Dementia	604
	Safer prescribing for physical conditions in dementia	631
	Management of behavioural and psychological symptoms	
	of dementia (BPSD)	644
	A guide to medication doses of commonly used psychotropics in older adults	657
	Covert administration of medicines within food and drink	667
	Treatment of depression in older people	673
Chapter 7	Pregnancy and breastfeeding	679
	Drug choice in pregnancy	679
	What to include in discussions with pregnant women	681
	Breastfeeding	702
Chapter 8	Hepatic and renal impairment	723
	Hepatic impairment	723
	Renal impairment	735
Part 3	Prescribing in specialist conditions	755
Chapter 9	Drug treatment of other psychiatric conditions	757
-	Borderline personality disorder (BPD)	757
	Eating disorders	761
	Delirium	767

Chapter 10	Drug treatment of psychiatric symptoms occurring in the	
	context of other disorders	777
	General principles of prescribing in HIV	777
	Epilepsy	785
	22q11.2 deletion syndrome	794
	Learning disabilities	797
	Huntington's disease – pharmacological treatment	803
	Multiple sclerosis	808
	Parkinson's disease	814
	Atrial fibrillation – using psychotropics	819
	Recommendations – psychotropics in AF	820
	Psychotropics in bariatric surgery	822
	Prescribing in patients with psychiatric illness at the end of life	829
Part 4	Other aspects of psychotropic drug use	831
Chapter 11	Pharmacokinetics	833
	Plasma level monitoring of psychotropic drugs	833
	Interpreting postmortem blood concentrations	847
	Acting on clozapine plasma concentration results	849
	Psychotropics and cytochrome (CYP) function	851
	Smoking and psychotropic drugs	856
	Drug interactions with alcohol	860
Chapter 12	Other substances	865
	Caffeine	865
	Nicotine	871
Chapter 13	Psychotropic drugs in special conditions	875
	Psychotropics in overdose	875
	Driving and psychotropic medicines	883
	Psychotropics and surgery	889
Chapter 14	Miscellany	897
	Enhancing medication adherence	897
	Re-starting psychotropic medications after a period of non-compliance	905
	Biochemical and haematological effects of psychotropics	907
	Summary of psychiatric side effects of non-psychotropics Prescribing drugs outside their licensed indications ('off-label'	917
	prescribing or unapproved use of approved drugs)	923
	Examples of acceptable use of drugs outside their product licences/labels	925
	The Mental Health Act in England and Wales	927
	Site of administration of intramuscular injections	932
	Intravenous formulations in psychiatry	937

943

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

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

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

CD7		DIVA	
CBZ	carbamazepine	DIVA	Diagnostic Interview for
CDRS	Children's Depression Rating	DID	DSM-IV ADHD
ODT	Scale	DLB	dementia with Lewy bodies
CDT	carbohydrate-deficient	DMDD	disruptive mood dysregulation
OF C	transferrin	Data	disorder
CES-D	Centre for Epidemiological	DOAC	direct-acting oral anticoagulant
~~~~	Studies Depression scale	DoLS	Deprivation of Liberty
CGAS	Children's Global Assessment		Safeguards
	Scale	DSM	Diagnostic and Statistical
CGI	Clinical Global Impression		Manual of Mental Disorders
	scales	DVLA	Driver and Vehicle Licensing
CI	confidence interval		Agency
CIBIC-Plus	Clinician's Interview-Based	EAD	early after depolarisation
	Impression of Change	ECG	electrocardiogram
CIGH	clozapine-induced gastrointesti-	ECT	electroconvulsive therapy
	nal hypomotility	EDTA	ethylenediaminetetraacetic acid
CIWA-Ar	Clinical Institute Withdrawal	EEG	electroencephalogram
	Assessment of Alcohol scale	eGFR	estimated glomerular filtration
	revised		rate
CK	creatine kinase	EMDR	eye movement desensitisation
CKD	chronic kidney disease		and reprocessing
CKD-EPI	Chronic Kidney Disease	EOSS	early-onset
	Epidemiology Collaboration		schizophrenia-spectrum
CNS	central nervous system	EPA	eicosapentanoic acid
COMT	catechol-O-methyltransferase	EPS	extrapyramidal symptoms
COPD	chronic obstructive pulmonary	ER	extended release
	disease	ERK	extracellular signal-regulated
COX	cyclo-oxygenase		kinase
СРК	creatinine phosphokinase	ERP	exposure and response
CPP	child-parent psychotherapy		prevention
CPSS	Child PTSD Symptom Scale	ES	effect size
CrCl	creatinine clearance	ESR	erythrocyte sedimentation rate
CREB	cAMP response element-binding	FAST	functional assessment staging
	protein	FBC	full blood count
CRP	C-reactive protein	FDA	Food and Drug Administration
CUtLASS	Cost Utility of the Latest		(USA)
	Antipsychotic Drugs in	FGA	first-generation antipsychotic
	Schizophrenia Study	FPG	fasting plasma glucose
CVA	cerebrovascular accident	FTI	Fatal Toxicity Index
CY-BOCS	Children's Yale-Brown Obsessive	GABA	γ-aminobutyric acid
	Compulsive Scale	GAD	generalised anxiety disorder
CYP	cytochrome P	GASS	Glasgow Antipsychotic
DAI	drug attitude inventory		Side-effect Scale
DESS	Discontinuation–Emergent Signs	GBL	gamma-butyrolactone
	and Symptoms scale	G-CSF	granulocyte colony-stimulating
DEXA	dual-energy X-ray		factor
	absorptiometry	GFR	glomerular filtration rate
DHEA	dehydroepiandrosterone	GGT	γ-glutamyl transferase
	, <u>1</u>		

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

PDD	pervasive developmental	SCARED	Screen for Child Anxiety and
PDD-NOS	disorders pervasive developmental	SCIRS	Related Emotional Disorders Severe Cognitive Impairment
100 1100	disorders not otherwise specified	Sento	Rating Scale
P-gp	P-glycoprotein	SCRA	synthetic cannabinoid receptor
PHQ-9	Patient Health Questionnaire-9		agonist
PICU	psychiatric intensive care unit	SGA	second-generation
PLC	pathological laughter and crying		antipsychotics
PLWH	people living with HIV	SIADH	syndrome of inappropriate
PMR	post-mortem redistribution		antidiuretic hormone
ро	<i>per os</i> (by mouth)	SIB	severe impairment battery
POMH-UK	Prescribing Observatory for	SJW	St. John's wort
	Mental Health	SLE	systemic lupus erythematosus
PPH	post-partum haemorrhage	SNRI	serotonin-noradrenaline
PPI	proton pump inhibitor		reuptake inhibitor
prn	pro re nata (as required)	SOAD	second opinion appointed
PT	prothrombin time		doctor
PTSD	post-traumatic stress disorder	SPC	summary of product
PWE	people with epilepsy		characteristics
qds	quarter die sumendum (four	SPECT	single photon emission
	times a day)		computed tomography
QTc	QT interval adjusted for heart	SROM	slow release oral morphine
	rate	SS	steady state
RC	responsible clinician	SSRI	selective serotonin reuptake
RCADS	Revised Children's Anxiety and		inhibitor
	Depression Scale	STAR*D	Sequenced Treatment
RCT	randomised controlled trial		Alternatives to Relieve
RID	relative infant dose		Depression programme
RIMA	reversible inhibitor of monoam-	STS	selegiline transdermal system
	ine oxidase A	TADS	Treatment of Adolescents with
RLAI	risperidone long-acting injection		Depression Study
ROMI	Rating of Medication Influences	TCA	tricyclic antidepressant
	scale	TD	tardive dyskinesia
RPG	random plasma glucose	tDCS	transcranial direct current
RR	relative risk		stimulation
RRBI	restricted repetitive behaviours	TDP	torsades de pointes
	and interests	tds	ter die sumendum (three times
RT	rapid tranquillisation		a day)
RTA	road traffic accident	TEAM	Treatment of Early Age Mania
rTMS	repetitive transcranial magnetic	TF-CBT	trauma-focused cognitive
	stimulation		behavioural therapy
RUPP	Research Units on Paediatric	TFT	thyroid function test
	Psychopharmacology	THC/CBD	tetrahydrocannabinol/
RYGB	Roux-en-Y gastric bypass		cannabidiol
SADQ	Severity of Alcohol Dependence	TIA	transient ischaemic attack
-	Questionnaire	TMS	transcranial magnetic
SAWS	Short Alcohol Withdrawal Scale		stimulation

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

## Drug treatment of major psychiatric conditions

## 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

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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 adherence² 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 health-care, 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 CATIE⁴ and CUtLASS⁵ 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 psychosis⁸ 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 individually.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-analysis¹³ 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 antipsychotics¹⁴ 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 schizophrenia¹⁷ 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 robust²⁶ (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. Timelimited 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 multiepisode 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.

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
lloperidone ^{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