The Maudsley

THE SOUTH LONDON AND MAUDSLEY NHS FOUNDATION TRUST
OXLEAS NHS FOUNDATION TRUST

# Prescribing Guidelines in Psychiatry

ELEVENTH EDITION

David Taylor
Carol Paton
Shitij Kapur

WILEY-BLACKWELL

# The Maudsley Prescribing Guidelines in Psychiatry

# The Maudsley Prescribing Guidelines in Psychiatry

11th Edition


**David Taylor**
Director of Pharmacy and Pathology
South London and Maudsley NHS Foundation Trust;
Professor of Psychopharmacology, King's College London, London, UK

**Carol Paton**
Chief Pharmacist, Oxleas NHS Foundation Trust
Honorary Research Fellow, Imperial College, London, UK

**Shitij Kapur**
Dean and Professor, Institute of Psychiatry
King's College London, London, UK



WILEY-BLACKWELL
A John Wiley & Sons, Ltd., Publication

Wiley-Blackwell is an imprint of John Wiley & Sons, formed by the merger of Wiley's global Scientific, Technical and Medical business with Blackwell Publishing.

*Registered office:* John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

*Editorial offices:* 9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

For details of our global editorial offices, for customer services and for information about how to apply for permission to reuse the copyright material in this book please see our website at www.wiley.com/wiley-blackwell



*Library of Congress Cataloging-in-Publication Data*

Taylor, David, 1946–
The Maudsley prescribing guidelines in psychiatry / David Taylor, Carol Paton, Shitij Kapur. – 11th ed.
p. ; cm.
Prescribing guidelines in psychiatry
Rev. ed. of: Prescribing guidelines. 2009.
Includes bibliographical references and index.
ISBN 978-0-470-97948-8 (pbk. : alk. paper)
I. Paton, Carol. II. Kapur, Shitij. III. Taylor, David, 1946– Prescribing guidelines. IV. South London and Maudsley NHS Trust. V. Title. VI. Title: Prescribing guidelines in psychiatry.
[DNLM: 1. Mental Disorders–drug therapy–Great Britain. 2. Psychopharmacology–methods–Great Britain. 3. Psychotropic Drugs–administration & dosage–Great Britain. 4. Psychotropic Drugs–therapeutic use–Great Britain. WM 402]
616.89′18–dc23

2011051662

A catalogue record for this book is available from the British Library.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Set in 10/12pt Minion by Aptara® Inc., New Delhi, India

Printed in [Country only]

1 2012

# Contents

# Preface

The publication of this 11th edition of *The Maudsley Prescribing Guidelines* marks the 18th year of its distribution. Back in 1994, the original idea behind the first edition was to provide evidence-based guidance on prescribing in common psychiatric conditions. At that time, there was almost no evidence-based guidance of any sort in this area and, partly as a consequence, treatment varied widely and prescribing practice was of somewhat variable quality. Today, of course, clinicians are swamped with prescribing guidance from various sources, many of them of high repute. Our task, then, in preparing this edition is partly to find commonality with and within other guidelines but also to provide guidance where there is none (inevitably the more obscure or arcane areas of practice). We have also tried to bring our guidelines broadly in line with those of UK NICE, notwithstanding the age of some of these publications and the small differences in opinion that are bound to arise over time.

This 11th edition includes significant changes from the previous edition. All sections have been updated to include data published before the end of 2011 and several new sections have been added. We also have a new publisher, Wiley–Blackwell, who have helped considerably in the formatting of this edition, improving the organisation and navigation.

As usual, thanks are due to a great many experts who have kindly contributed to *The Guidelines* (listed on the next page) without whom *The Guidelines* could not exist. We are also sincerely grateful to Joan Marsh at Wiley–Blackwell and to Maria O'Hagan who has managed the production of this and previous editions and who maintains a growing database of over 15,000 scientific references essential for the production of *The Guidelines*.

*David Taylor*

# Acknowledgements

We are deeply indebted to previous contributors and to the following contributors to the present edition of *The Maudsley Prescribing Guidelines*.

Ayesha Ali
Azizah Attard
Sube Banerjee
James Bell
Delia Bishara
Tony Cleare
Anne Connolly
Richard Corrigall
Sarah Curran
Vivienne Curtis
Vandana Dimri
Michael Dixon
Petrina Douglas-Hall
Andrew Easton
Sarah Elliott
Emily Finch
Andrew Flynn
Russell Foster
Paul Gringras
Isobel Heyman
Rob Howard
Ann Hyatt
Bimpe Idowu
Francis Keaney
Mike Kelleher
Shubhra Mace
Jane Marshall
Gordana Milavic
Ify Okonkwo
Banke Olofinjana
Carmine Pariante
Maxine Patel
Sally Porter
Kylie Reed
Paramala J Santosh
Anna Sparshatt
Argyris Stringaris
Gay Sutherland
Eric Taylor
Helen Turner
Seema Varma
Eromona Whiskey

## Notes on using *The Maudsley Prescribing Guidelines*

The main aim of *The Maudsley Prescribing Guidelines* is to provide clinicians with practically useful advice on the prescribing of psychotropic agents in 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 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 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 up to December 2011. Much of the advice contained here will become outdated 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 Maudsley Prescribing 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 December 2011. Thus, we have included, for example, ziprasidone and iloperidone, even though these drugs are not marketed in the UK at this time. Their inclusion gives *The Guidelines* relevance in those countries where ziprasidone and iloperidone are marketed and may also be of benefit to UK readers, since many unlicensed drugs can be obtained through formal pharmaceutical importers. We have also included information on drugs likely to be introduced into practice in the next two years. Many older drugs or those not widely available (methotrimeprazine, pericyazine, maprotiline, zotepine, 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.

# List of abbreviations

| | |
|---|---|
| ACE | angiotensin-converting enzyme |
| ACh | acetylcholine |
| AChE | acetylcholinesterase |
| AD | Alzheimer's disease |
| ADAS-cog | Alzheimer's Disease Assessment Scale – cognitive subscale |
| ADH | alcohol dehydrogenase/antidiuretic hormone |
| ADHD | attention deficit hyperactivity disorder |
| ADL | Activities of Daily Living |
| ADR | adverse drug reaction |
| ALT | alanine aminotransferase |
| ASD | autism spectrum disorders |
| AST | aspartate aminotransferase |
| BAD | bipolar affective disorder |
| BAP | British Association for Psychopharmacology |
| BDNF | brain-derived neurotrophic factor |
| BMI | Body Mass Index |
| *BNF* | *British National Formulary* |
| BP | blood pressure |
| BPD | borderline personality disorder |
| bpm | beats per minute |
| BuChE | butyrylcholinesterase |
| CBT | cognitive behaviour therapy |
| CI | confidence interval |
| CIWA-Ar | Clinical Institute Withdrawal Assessment of Alcohol Scale Revised |
| CK | creatine kinase |
| CNS | central nervous system |
| COMT | catechol-*O*-methyltransferase |
| COX | cyclo-oxygenase |
| CSM | Committee on Safety of Medicines |
| CYP | cytochrome P450 |
| DAI | Drug Attitude Inventory |
| DHA | docosahexanoic acid |
| DHEA | dehydroepiandrosterone |
| DLB | dementia with Lewy bodies |
| DSM | *Diagnostic and Statistical Manual of Mental Disorders* |
| DT | delirium tremens |
| DVLA | Driver and Vehicle Licensing Agency |
| ECG | electrocardiogram |
| ECT | electroconvulsive treatment |
| EEG | electroencephalogram |
| eGFR | estimated GFR |
| EPA | eicosapentanoic acid |
| EPS | extrapyramidal side-effects |
| ERK | extracellular signal-regulated kinase |
| FBC | full blood count |
| FDA | Food and Drug Administration |
| 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 | γ-butaryl-lactone |
| G-CSF | granulocyte-colony stimulating factor |
| GFR | glomerular filtration rate |
| GGT | γ-glutamyl transferase |
| GHB | γ-hydroxybutyrate |
| GI | gastrointestinal |
| GIT | gastrointestinal tract |
| GM-CSF | granulocyte macrophage colony-stimulating factor |
| HDL | high-density lipoprotein |
| HR | hazard ratio |
| *ICD* | *International Classification of Diseases* |
| IM | intramuscular |
| INR | international normalised ratio |
| IV | intravenous |
| LAI | long-acting injection |
| LD | learning disability |
| LDL | low-density lipoprotein |
| LFT | liver function test |
| LUNSERS | Liverpool University Neuroleptic Side-Effect Ratings Scale |
| MAO-A | monoamine oxidase A |
| MAOI | monoamine oxidase inhibitor |
| MCI | mild cognitive impairment |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MI | myocardial infarction |
| MMSE | Mini Mental State Examination |
| NICE | National Institute for Health and Clinical Excellence |
| NMDA | N-methyl-D-aspartate |
| NMS | neuroleptic malignant syndrome |
| NNT | number needed to treat |
| NRT | nicotine replacement therapy |
| NSAID | non-steroidal anti-inflammatory drug |
| OCD | obsessive compulsive disorder |
| OGTT | oral glucose tolerance test |
| PANDAS | Paediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus |
| PDD–NOS | pervasive developmental disorders–not otherwise specified |
| PEG | percutaneous endoscopic gastrostomy |
| POMH-UK | Prescribing Observatory for Mental Health - UK |
| prn | *pro re nata* |
| PTSD | post-traumatic stress disorder |
| PUFA | polyunsaturated fatty acid |
| RCT | randomised controlled trial |
| RLAI | risperidone long-acting injection |
| RRBI | restricted repetitive behaviours and interests |
| SADQ | Severity of Alcohol Dependence Questionnaire |
| SAWS | Short Alcohol Withdrawal Scale |
| SGA | second-generation antipsychotic |
| SIADH | syndrome of inappropriate secretion of antidiuretic hormone |
| SJW | St John's wort |
| SPC | Summary of Product Characteristics |
| SPECT | single photon emission computed tomography |
| SSRI | selective serotonin reuptake inhibitor |
| STAR-D | Sequenced Treatment Alternatives to Relieve Depression |
| TCA | tricyclic antidepressant |
| TD | tardive dyskinesia |
| TFT | thyroid function test |
| TORDIA | Treatment of Resistant Depression in Adolescence |
| UGT | UDP-glucuronosyl transferase |
| VTE | venous thromboembolism |
| WCC | white cell count |
| YMRS | Young Mania Rating Scale |

# Chapter 1

# Plasma level monitoring of psychotropic drugs and anticonvulsants

Plasma drug concentration or plasma 'level' monitoring is a process surrounded by some confusion and misunderstanding. Drug level monitoring, when appropriately used, is of considerable help in optimising treatment and assuring adherence. However, in psychiatry, as in other areas of medicine, plasma level determinations are frequently undertaken without good cause and results acted upon inappropriately.[1] Conversely, in other instances, plasma concentrations are underused.

Before taking a blood sample for plasma level assay, check the following.

- **Is there a clinically useful assay method available?** Only a minority of drugs have available assays. The assay must be clinically validated and results available within a clinically useful timescale.
- **Is the drug at 'steady state'?** Plasma levels are usually meaningful only when samples are taken after steady-state levels have been achieved. This takes 4–5 drug half-lives.
- **Is the timing of the sample correct?** Sampling time is vitally important for many but not all drugs. If the recommended sampling time is, say, 12 h post dose, then the sample should be taken 11–13 h post dose if possible; 10–14 h post dose, if absolutely necessary. For trough or 'predose' samples, take the blood sample immediately before the next dose is due. Do not, under any circumstances, withhold the next dose for more than 1 or (possibly) 2 h until a sample is taken. Withholding for longer than this will inevitably give a misleading result (it will give a lower result than ever seen in the usual, regular dosing), which may lead to an inappropriate dose increase. Sampling time is less critical with drugs with a long half-life

*The Maudsley Prescribing Guidelines in Psychiatry*, Eleventh Edition. David Taylor, Carol Paton and Shitij Kapur.

(e.g. olanzapine) but, as an absolute minimum, prescribers should always record the time of sampling and time of last dose.

If a sample is not taken within 1–2 h of the required time, it has the potential to mislead rather than inform. The only exception to this is if toxicity is suspected – sampling at the time of suspected toxicity is obviously appropriate.

- **Will the level have any inherent meaning?** Is there a target range of plasma levels? If so, then plasma levels (from samples taken at the right time) will usefully guide dosing. If there is not an accepted target range, plasma levels can only indicate adherence or potential toxicity. If the sample is being used to check compliance, bear in mind that a plasma level of zero indicates only that the drug has not been taken in the past several days. Plasma levels above zero may indicate erratic compliance, full compliance or even long-standing non-compliance disguised by recent taking of prescribed doses. Note also that target ranges have their limitations: patients may respond to lower levels than the quoted range and tolerate levels above the range; also, ranges quoted by different laboratories sometimes vary widely without explanation.
- **Is there a clear reason for plasma level determination?** Only the following reasons are valid:
  - to confirm compliance (but see above)
  - if toxicity is suspected
  - if a pharmacokinetic drug interaction is suspected
  - if clinical response is difficult to assess directly (and where a target range of plasma levels has been established)
  - if the drug has a narrow therapeutic index and toxicity concerns are considerable.

## Interpreting sample results

The basic rule for sample level interpretation is to act upon assay results in conjunction with reliable clinical observation ('*treat the patient, not the level*'). For example, if a patient is responding adequately to a drug but has a plasma level below the accepted target range, then the dose should not normally be increased. If a patient has intolerable adverse effects but a plasma level within the target range, then a dose decrease may be appropriate.

Where a plasma level result is substantially different from previous results, a repeat sample is usually advised. Check dose, timing of dose and recent compliance but ensure, in particular, the correct timing of the sample. Many anomalous results are the consequence of changes in sample timing.

Table 1.1 shows the target ranges for some commonly prescribed psychotropic drugs.

**Table 1.1** Interpreting plasma concentration sample results for psychotropic drugs

| Drug | Target range | Sample timing | Time to steady state | Comments |
|---|---|---|---|---|
| Amisulpride | 200–320 μg/l | Trough | 3 days | See text |
| Aripiprazole | 150–210 μg/l | Trough | 15–16 days | See text |
| Carbamazepine[2,3] | >7 mg/l bipolar disorder | Trough | 2 weeks | Induces its own metabolism. Time to steady state dependent on autoinduction |
| Clozapine | 350–500 μg/l<br>Upper limit of target range is ill defined | Trough (12 h post-dose if once daily) | 2–3 days | See text |
| Lamotrigine[4–7] | Not established but suggest 2.5–15 mg/l | Trough | 5 days<br>Auto-induction is thought to occur, so time to steady state may be longer | Some debate over utility of lamotrigine levels, especially in bipolar disorder. Toxicity may be increased above 15 mg/l |
| Lithium[8–11] | 0.6–1.0 mmol/l (may be >1.0 mmol/l in mania) | 12 h post dose | 3–5 days | Well-established target range |
| Olanzapine | 20–40 μg/l | 12 h | 1 week | See text |
| Paliperidone[12] | 20–60 μg/l<br>(9-OH risperidone) | Trough | 2–3 days oral<br>2 months depot | No obvious reason to suspect range should be any different from risperidone. Some practical confirmation |
| Phenytoin[3] | 10–20 mg/l | Trough | Variable | Follows zero-order kinetics. Free levels may be useful |
| Quetiapine | Around 50-100 μg/l? | Trough? | 2–3 days oral | Target range not defined. Plasma level monitoring not recommended. See text |

(*Continued*)

**Table 1.1** (*Continued*)

| Drug | Target range | Sample timing | Time to steady state | Comments |
|---|---|---|---|---|
| Risperidone | 20–60 μg/l (active moiety – risperidone + 9-OH risperidone) | Trough | 2–3 days oral, 6–8 weeks injection | Plasma level monitoring is not recommended. See text |
| Tricyclics[13] | Nortriptyline 50–150 μg/l Amitriptyline 100–200 μg/l | Trough | 2–3 days | Rarely used and of dubious benefit. Use ECG to assess toxicity |
| Valproate[2, 3, 14–17] | 50–100 mg/l Epilepsy and bipolar | Trough (if once daily at night, sample at 12–24 h) | 2–3 days | Some doubt over value of levels in epilepsy and in bipolar disorder. Some evidence that levels up to 125 mg/l are tolerated and more effective than lower levels (in mania) |

ECG, electrocardiogram.

## Amisulpride

Amisulpride plasma levels are closely related to dose with insufficient variation to recommend routine plasma level monitoring. Higher levels observed in women[18–20] and older patients[18,20] seem to have little significant clinical implication for either therapeutic response or adverse effects. A (trough) threshold for clinical response has been suggested to be approximately 100 μg/l;[21] mean levels of 367 μg/l[20] have been noted in responders in individual studies. Adverse effects (notably extrapyramidal side-effects [EPS]) have been observed at mean levels of 336 μg/l,[18] 377 μg/l[21] and 395 μg/l.[19] A plasma level threshold of below 320 μg/l has been found to predict avoidance of EPS.[21] A review of the current literature[22] has suggested an approximate range of **200–320 μg/l** for optimal clinical response and avoidance of adverse effects.

In practice, amisulpride plasma level monitoring is rarely undertaken and few laboratories offer amisulpride assays. The dose–response relationship is sufficiently robust to obviate the need for plasma sampling within the licensed dose range; adverse effects are well managed by dose adjustment alone. Plasma level monitoring is best reserved for those in whom clinical response is poor, adherence is questioned and in whom drug interactions or physical illness may make adverse effects more likely.

## Aripiprazole

Plasma level monitoring of aripiprazole is rarely carried out in practice. The dose–response relationship of aripiprazole is well established, with a plateau in clinical response and $D_2$ dopamine occupancy seen at doses above approximately 10 mg/day.[23] Plasma levels of aripiprazole, its metabolite and the total moiety (parent plus metabolite) strongly relate linearly to dose, making it possible to predict, with some certainty, an approximate plasma level for a given dose.[24] Target plasma level ranges for optimal clinical response have been suggested as 146–254 μg/l[25] and 150–300 μg/l,[26] with adverse effects observed above 210 μg/l.[26] Interindividual variation in aripiprazole plasma levels has been observed but not fully investigated, although gender appears to have little influence.[27,28] Age, metabolic enzyme genotype and interacting medications seem likely causes of variation[26–29] but there are too few reports regarding their clinical implication to recommend specific monitoring in respect to factors. A putative range of **150–210 μg/l**[24] has been suggested as a target for patients taking aripiprazole who are showing little or no clinical response or who have intolerable EPS. For reasons described here, plasma level monitoring is not advised in routine practice.

## Clozapine

Clozapine plasma levels are broadly related to daily dose[30] but there is sufficient variation to make any precise prediction of plasma level impossible. Plasma levels are generally lower in younger patients, males[31] and smokers[32] and higher in Asians.[33] A series of algorithms has been developed for the approximate prediction of clozapine levels according to patient factors and these are strongly recommended.[34] Algorithms cannot, however, account for other influences on clozapine plasma levels such as changes in adherence, inflammation[35] and infection.[36]

The plasma level threshold for acute response to clozapine has been suggested to be 200 μg/l,[37] 350 μg/l,[38–40] 370 μg/l,[41] 420 μg/l,[42] 504 μg/l[43] and 550 μg/l.[44] Limited data suggest that a level of at least 200 μg/l is required to prevent relapse.[45] Substantial variation in clozapine plasma level may also predict relapse.[46]

Despite these varied estimates of response threshold, plasma levels can be useful in optimising treatment. In those not responding to clozapine, dose should be adjusted to give plasma levels in the range **350–500 μg/l**. Those not tolerating clozapine may benefit from a reduction to a dose giving plasma levels in this range. An upper limit to the clozapine target range has not been defined. Plasma levels do seem to predict electroencephalogram (EEG) changes[47,48] and seizures occur more frequently in patients with levels above 1000 μg/l[49] so levels should probably be kept well below this. Other non-neurological clozapine-related adverse effects also seem to be related to plasma-level,[50] as might be expected. Note that clozapine metabolism may become saturated at higher doses: the ratio of clozapine to norclozapine increases with increasing plasma levels, suggesting saturation.[51–53] The effect of fluvoxamine also suggests that metabolism via CYP1A2 to norclozapine can be overwhelmed.[54]

Placing an upper limit on the target range for clozapine levels may discourage potentially worthwhile dose increases within the licensed dose range. Before plasma levels were widely used, clozapine was fairly often given in doses up to 900 mg/day, with valproate being added

when the dose reached 600 mg/day. It remains unclear whether using these high doses can benefit patients with plasma levels already above the accepted threshold. Nonetheless, it is prudent to use an anticonvulsant as prophylaxis against seizures and myoclonus when plasma levels are above 500–600 μg/l and certainly when levels approach 1000 μg/l.

## Olanzapine

Plasma levels of olanzapine are linearly related to daily dose, but there is substantial variation,[55] with higher levels seen in women,[43] non-smokers[56] and those on enzyme-inhibiting drugs.[56,57] With once-daily dosing, the threshold level for response in schizophrenia has been suggested to be 9.3 μg/l (trough sample),[58] 23.2 μg/l (12-h postdose sample)[43] and 23 μg/l at a mean of 13.5 h post dose.[59] There is evidence to suggest that levels greater than around 40 μg/l (12-h sampling) produce no further therapeutic benefit than lower levels.[60] Severe toxicity is uncommon but may be associated with levels above 100 μg/l, and death is occasionally seen at levels above 160 μg/l[61] (albeit when other drugs or physical factors are relevant). A target range for therapeutic use of **20–40 μg/l** (12-h postdose sample) has been proposed[62] for schizophrenia; the range for mania is probably similar.[63]

Significant weight gain seems most likely to occur in those with plasma levels above 20 μg/l.[64] Constipation, dry mouth and tachycardia also seem to be related to plasma level.[65]

In practice, the dose of olanzapine should be governed by response and tolerability. Plasma level determinations should be reserved for those suspected of non-adherence or those not responding to the maximum licensed dose (at 20 mg/day, around 20% of patients will have olanzapine levels <20 μg/l).[66] In the latter case, dose may then be adjusted to give 12-h plasma levels of 20–40 μg/l.

## Quetiapine (IR)

Dose of quetiapine is weakly related to trough plasma concentration.[67–69] Mean levels reported within the dose range 150 mg/day to 800 mg/day range from 27 μg/l to 387 μg/l,[68,70–74] although the highest and lowest levels are not necessarily found at the lowest and highest doses. Age, gender and co-medication may contribute to the significant interindividual variance observed in therapeutic drug monitoring studies, with female gender,[74,75] older age[73,74] and CYP3A4-inhibiting drugs[68,73,74] likely to increase quetiapine concentration. Reports of these effects are conflicting[75–78] and not sufficient to support the routine use of plasma level monitoring based on these factors alone. Thresholds for clinical response have been proposed as **77 μg/l**[76,77] and **50–100 μg/l**;[78] EPS has been observed in females with levels in excess of 210 μg/l.[76,77] Despite the substantial variation in plasma levels at each dose, there is insufficient evidence to suggest a target therapeutic range, so plasma level monitoring has little value.

Most current reports of quetiapine concentrations are from trough samples. Because of the short half-life of quetiapine, trough levels tend to drop to within a relatively small range regardless of dose and previous peak level. Thus peak plasma levels may be more closely related to dose and clinical response[69] although monitoring of such is not currently justified in the absence of an established peak plasma target range. Quetiapine has an established

dose–response relationship and appears to be well tolerated at doses well beyond the licensed dose range.[79] In practice, dose adjustment should be based on patient response and tolerability.

## Risperidone

Risperidone plasma levels are rarely measured in the UK and very few laboratories have developed assay methods for its determination. Plasma level monitoring is probably unproductive (dose–response is well described) except where compliance is in doubt and in such cases, measurement of prolactin will give some idea of compliance.

The therapeutic range for risperidone is generally agreed to be **20–60 μg/l** of the active moiety (risperidone + 9-OH risperidone)[80,81] although other ranges (25–150 μg/l and 25–80 μg/l) have been proposed.[82] Plasma levels of 20–60 μg/l are usually afforded by oral doses of between 3 mg and 6 mg a day.[80,83–85] Occupancy of striatal dopamine $D_2$ receptors has been shown to be around 65% (the minimum required for therapeutic effect) at plasma levels of approximately 20 μg/l.[81]

Risperidone long-acting injection (25 mg/2 weeks) appears to result in plasma levels averaging between 4.4 and 22.7 μg/l.[84] Dopamine $D_2$ occupancies at this dose have been variously estimated at between 25% and 71%.[81,86,87] There is considerable interindividual variation around these mean values, with a substantial minority of patients with plasma levels above those shown. Nonetheless, these data do cast doubt on the efficacy of a dose of 25 mg/2 weeks[84] although it is noteworthy that there is some evidence that long-acting preparations are effective despite apparently subtherapeutic plasma levels and dopamine occupancies.[88]

## References


1. Mann K et al. Appropriateness of therapeutic drug monitoring for antidepressants in routine psychiatric inpatient care. Ther Drug Monit 2006; **28**:83–88.
2. Taylor D et al. Doses of carbamazepine and valproate in bipolar affective disorder. Psychiatr Bull 1997; **21**:221–223.
3. Eadie MJ. Anticonvulsant drugs. Drugs 1984; **27**:328–363.
4. Cohen AF et al. Lamotrigine, a new anticonvulsant: pharmacokinetics in normal humans. Clin Pharmacol Ther 1987; **42**:535–541.
5. Kilpatrick ES et al. Concentration-effect and concentration-toxicity relations with lamotrigine: a prospective study. Epilepsia 1996; **37**:534–538.
6. Johannessen SI et al. Therapeutic drug monitoring of the newer antiepileptic drugs. Ther Drug Monit 2003; **25**:347–363.
7. Lardizabal DV et al. Tolerability and pharmacokinetics of oral loading with lamotrigine in epilepsy monitoring units. Epilepsia 2003; **44**:536–539.
8. Schou M. Forty years of lithium treatment. Arch Gen Psychiatry 1997; **54**:9–13.
9. Anon. Using lithium safely. Drug Ther Bull 1999; **37**:22–24.
10. Nicholson J et al. Monitoring patients on lithium – a good practice guideline. Psychiatr Bull 2002; **26**:348–351.
11. National Institute for Health and Clinical Excellence. Bipolar disorder. The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. Clinical Guidance 38. 2006. www.nice.org.uk .
12. Nazirizadeh Y et al. Serum concentrations of paliperidone versus risperidone and clinical effects. Eur J Clin Pharmacol 2010; **66**:797–803.
13. Taylor D et al. Plasma levels of tricyclics and related antidepressants: are they necessary or useful? Psychiatr Bull 1995; **19**:548–550.
14. Davis R et al. Valproic acid – a reappraisal of its pharmacological properties and clinical efficacy in epilepsy. Drugs 1994; **47**:332–372.
15. Perucca E. Pharmacological and therapeutic properties of valproate. CNS Drugs 2002; **16**:695–714.
16. Allen MH et al. Linear relationship of valproate serum concentration to response and optimal serum levels for acute mania. Am J Psychiatry 2006; **163**:272–275.
17. Bowden CL et al. Relation of serum valproate concentration to response in mania. Am J Psychiatry 1996; **153**:765–770.

18. Muller MJ et al. Amisulpride doses and plasma levels in different age groups of patients with schizophrenia or schizoaffective disorder. J Psychopharmacol 2008; **23**:278–286.
19. Muller MJ et al. Gender aspects in the clinical treatment of schizophrenic inpatients with amisulpride: a therapeutic drug monitoring study. Pharmacopsychiatry 2006; **39**:41–46.
20. Bergemann N et al. Plasma amisulpride levels in schizophrenia or schizoaffective disorder. Eur Neuropsychopharmacol 2004; **14**: 245–250.
21. Muller MJ et al. Therapeutic drug monitoring for optimizing amisulpride therapy in patients with schizophrenia. J Psychiatr Res 2007; **41**:673–679.
22. Sparshatt A et al. Amisulpride – dose, plasma concentration, occupancy and response: implications for therapeutic drug monitoring. Acta Psychiatr Scand 2009; **120**:416–428.
23. Mace S et al. Aripiprazole: dose–response relationship in schizophrenia and schizoaffective disorder. CNS Drugs 2008; **23**:773–780.
24. Sparshatt A et al. A systematic review of aripiprazole – dose, plasma concentration, receptor occupancy and response: implications for therapeutic drug monitoring. J Clin Psychiatry 2010; **17**:1447–1456.
25. Kirschbaum KM et al. Therapeutic monitoring of aripiprazole by HPLC with column-switching and spectrophotometric detection. Clin Chem 2005; **51**:1718–1721.
26. Kirschbaum KM et al. Serum levels of aripiprazole and dehydroaripiprazole, clinical response and side effects. World J Biol Psychiatry 2008; **9**:212–218.
27. Molden E et al. Pharmacokinetic variability of aripiprazole and the active metabolite dehydroaripiprazole in psychiatric patients. Ther Drug Monit 2006; **28**:744–749.
28. Bachmann CJ et al. Large variability of aripiprazole and dehydroaripiprazole serum concentrations in adolescent patients with schizophrenia. Ther Drug Monit 2008; **30**:462–466.
29. Hendset M et al. Impact of the CYP2D6 genotype on steady-state serum concentrations of aripiprazole and dehydroaripiprazole. Eur J Clin Pharmacol 2007; **63**:1147–1151.
30. Haring C et al. Influence of patient-related variables on clozapine plasma levels. Am J Psychiatry 1990; **147**:1471–1475.
31. Haring C et al. Dose-related plasma levels of clozapine: influence of smoking behaviour, sex and age. Psychopharmacology 1989; **99**(Suppl):S38–S40.
32. Taylor D. Pharmacokinetic interactions involving clozapine. Br J Psychiatry 1997; **171**:109–112.
33. Ng CH et al. An inter-ethnic comparison study of clozapine dosage, clinical response and plasma levels. Int Clin Psychopharmacol 2005; **20**:163–168.
34. Rostami-Hodjegan A et al. Influence of dose, cigarette smoking, age, sex, and metabolic activity on plasma clozapine concentrations: a predictive model and nomograms to aid clozapine dose adjustment and to assess compliance in individual patients. J Clin Psychopharmacol 2004; **24**:70–78.
35. Haack MJ et al. Toxic rise of clozapine plasma concentrations in relation to inflammation. Eur Neuropsychopharmacol 2003; **13**:381–385.
36. De Leon J et al. Serious respiratory infections can increase clozapine levels and contribute to side effects: a case report. Prog Neuropsychopharmacol Biol Psychiatry 2003; **27**:1059–1063.
37. VanderZwaag C et al. Response of patients with treatment-refractory schizophrenia to clozapine within three serum level ranges. Am J Psychiatry 1996; **153**:1579–1584.
38. Perry PJ et al. Clozapine and norclozapine plasma concentrations and clinical response of treatment refractory schizophrenic patients. Am J Psychiatry 1991; **148**:231–235.
39. Miller DD. Effect of phenytoin on plasma clozapine concentrations in two patients. J Clin Psychiatry 1991; **52**:23–25.
40. Spina E et al. Relationship between plasma concentrations of clozapine and norclozapine and therapeutic response in patients with schizophrenia resistant to conventional neuroleptics. Psychopharmacology 2000; **148**:83–89.
41. Hasegawa M et al. Relationship between clinical efficacy and clozapine concentrations in plasma in schizophrenia: effect of smoking. J Clin Psychopharmacol 1993; **13**:383–390.
42. Potkin SG et al. Plasma clozapine concentrations predict clinical response in treatment-resistant schizophrenia. J Clin Psychiatry 1994; **55** (Suppl B):133–136.
43. Perry PJ. Therapeutic drug monitoring of antipsychotics. Psychopharmacol Bull 2001; **35**:19–29.
44. Llorca PM et al. Effectiveness of clozapine in neuroleptic-resistant schizophrenia: clinical response and plasma concentrations. J Psychiatry Neurosci 2002; **27**:30–37.
45. Xiang YQ et al. Serum concentrations of clozapine and norclozapine in the prediction of relapse of patients with schizophrenia. Schizophr Res 2006; **83**:201–210.
46. Stieffenhofer V et al. Clozapine plasma level monitoring for prediction of rehospitalization schizophrenic outpatients. Pharmacopsychiatry 2011; **44**:55–59.
47. Khan AY et al. Examining concentration-dependent toxicity of clozapine: role of therapeutic drug monitoring. J Psychiatr Pract 2005; **11**:289–301.
48. Varma S et al. Clozapine-related EEG changes and seizures: dose and plasma-level relationships. Ther Adv Psychopharmacol 2011; **1**:47–66.
49. Greenwood-Smith C et al. Serum clozapine levels: a review of their clinical utility. J Psychopharmacol 2003; **17**:234–238.

50. Yusufi B et al. Prevalence and nature of side effects during clozapine maintenance treatment and the relationship with clozapine dose and plasma concentration. Int Clin Psychopharmacol 2007; **22**:238–243.
51. Volpicelli SA et al. Determination of clozapine, norclozapine, and clozapine-N-oxide in serum by liquid chromatography. Clin Chem 1993; **39**:1656–1659.
52. Guitton C et al. Clozapine and metabolite concentrations during treatment of patients with chronic schizophrenia. J Clin Pharmacol 1999; **39**:721–728.
53. Palego L et al. Clozapine, norclozapine plasma levels, their sum and ratio in 50 psychotic patients: influence of patient-related variables. Prog Neuropsychopharmacol Biol Psychiatry 2002; **26**:473–480.
54. Wang CY et al. The differential effects of steady-state fluvoxamine on the pharmacokinetics of olanzapine and clozapine in healthy volunteers. J Clin Pharmacol 2004; **44**:785–792.
55. Aravagiri M et al. Plasma level monitoring of olanzapine in patients with schizophrenia: determination by high-performance liquid chromatography with electrochemical detection. Ther Drug Monit 1997; **19**:307–313.
56. Gex-Fabry M et al. Therapeutic drug monitoring of olanzapine: the combined effect of age, gender, smoking, and comedication. Ther Drug Monit 2003; **25**:46–53.
57. Bergemann N et al. Olanzapine plasma concentration, average daily dose, and interaction with co-medication in schizophrenic patients. Pharmacopsychiatry 2004; **37**:63–68.
58. Perry PJ et al. Olanzapine plasma concentrations and clinical response in acutely ill schizophrenic patients. J Clin Psychopharmacol 1997; **6**:472–477.
59. Fellows L et al. Investigation of target plasma concentration–effect relationships for olanzapine in schizophrenia. Ther Drug Monit 2003; **25**:682–689.
60. Mauri MC et al. Clinical outcome and olanzapine plasma levels in acute schizophrenia. Eur Psychiatry 2005; **20**:55–60.
61. Rao ML et al. [Olanzapine: pharmacology, pharmacokinetics and therapeutic drug monitoring]. Fortschr Neurol Psychiatr 2001; **69**:510–517.
62. Robertson MD et al. Olanzapine concentrations in clinical serum and postmortem blood specimens – when does therapeutic become toxic? J Forensic Sci 2000; **45**:418–421.
63. Bech P et al. Olanzapine plasma level in relation to antimanic effect in the acute therapy of manic states. Nord J Psychiatry 2006; **60**:181–182.
64. Perry PJ et al. The association of weight gain and olanzapine plasma concentrations. J Clin Psychopharmacol 2005; **25**:250–254.
65. Kelly DL et al. Plasma concentrations of high-dose olanzapine in a double-blind crossover study. Hum Psychopharmacol 2006; **21**: 393–398.
66. Patel MX et al. Plasma olanzapine in relation to prescribed dose and other factors. Data from a therapeutic drug monitoring service, 1999–2009. Psychopharmacology 2011; **31**:1–7.
67. Gerlach M et al. Therapeutic drug monitoring of quetiapine in adolescents with psychotic disorders. Pharmacopsychiatry 2007; **40**: 72–76.
68. Hasselstrom J et al. Quetiapine serum concentrations in psychiatric patients: the influence of comedication. Ther Drug Monit 2004; **26**:486–491.
69. Sparshatt A et al. Relationship between daily dose, plasma concentrations, dopamine receptor occupancy, and clinical response to quetiapine: a review. J Clin Psychiatry 2011; **72**:1108–1123.
70. Winter HR et al. Steady-state pharmacokinetic, safety, and tolerability profiles of quetiapine, norquetiapine, and other quetiapine metabolites in pediatric and adult patients with psychotic disorders. J Child Adolesc Psychopharmacol 2008; **18**:81–98.
71. Li KY et al. Multiple dose pharmacokinetics of quetiapine and some of its metabolites in Chinese suffering from schizophrenia. Acta Pharmacol Sin 2004; **25**:390–394.
72. McConville BJ et al. Pharmacokinetics, tolerability, and clinical effectiveness of quetiapine fumarate: an open-label trial in adolescents with psychotic disorders. J Clin Psychiatry 2000; **61**:252–260.
73. Castberg I et al. Quetiapine and drug interactions: evidence from a routine therapeutic drug monitoring service. J Clin Psychiatry 2007; **68**:1540–1545.
74. Aichhorn W et al. Influence of age, gender, body weight and valproate comedication on quetiapine plasma concentrations. Int Clin Psychopharmacol 2006; **21**:81–85.
75. Mauri MC et al. Two weeks' quetiapine treatment for schizophrenia, drug-induced psychosis and borderline personality disorder: a naturalistic study with drug plasma levels. Expert Opin Pharmacother 2007; **8**:2207–2213.
76. Dragicevic A, Muller MJ, Sachse J, Hartter S, Hiemke C. Therapeutic drug monitoring (TDM) of quetiapine. Lecture presented at the Symposium of the AGNP, October 8–10th 2003, Munich.
77. Dragicevic A, Sachse J, Hartter S, Hiemke C, Muller MJ. Serum concentrations of quetiapine and clinical effects. International Meeting on Pharmacovigilance in Psychiatry, Therapeutic Drug Monitoring and Pharmacogenetics of Psychotropic Drugs, September 1–3 2005, Lausanne, Switzerland.
78. Dragicevic A, Trotzauer D, Hiemke C, Muller MJ. Gender and age effects on quetiapine serum concentrations in patients with schizophrenia or schizoaffective disorders. Lecture presented at the 24th Symposium of the AGNP, October 5–8th 2005, Munich.
79. Sparshatt A et al. Quetiapine: dose–response relationship in schizophrenia. CNS Drugs 2008; **22**:49–68.
80. Olesen OV et al. Serum concentrations and side effects in psychiatric patients during risperidone therapy. Ther Drug Monit 1998; **20**:380–384.

81. Remington G et al. A PET study evaluating dopamine D2 receptor occupancy for long-acting injectable risperidone. Am J Psychiatry 2006; **163**:396–401.
82. Seto K et al. Risperidone in schizophrenia: is there a role for therapeutic drug monitoring? Ther Drug Monit 2011; **33**:275–283.
83. Lane HY et al. Risperidone in acutely exacerbated schizophrenia: dosing strategies and plasma levels. J Clin Psychiatry 2000; **61**:209–214.
84. Taylor D. Risperidone long-acting injection in practice – more questions than answers? Acta Psychiatr Scand 2006; **114**:1–2.
85. Nyberg S et al. Suggested minimal effective dose of risperidone based on PET-measured D2 and 5-HT2A receptor occupancy in schizophrenic patients. Am J Psychiatry 1999; **156**:869–875.
86. Medori R et al. Plasma antipsychotic concentration and receptor occupancy, with special focus on risperidone long-acting injectable. Eur Neuropsychopharmacol 2006; **16**:233–240.
87. Gefvert O et al. Pharmacokinetics and D2 receptor occupancy of long-acting injectable risperidone (Risperdal Consta™) in patients with schizophrenia. Int J Neuropsychopharmacol 2005; **8**:27–36.
88. Nyberg S et al. D2 dopamine receptor occupancy during low-dose treatment with haloperidol decanoate. Am J Psychiatry 1995; **152**:173–178.

# Chapter 2

# Schizophrenia

The National Institute for Health and Clinical Excellence (NICE) guideline for medicines adherence[1] 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.[2]

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.

## Antipsychotic drugs

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

### Relative efficacy

Further to the publication of CATIE[3] and CUtLASS,[4] the World Psychiatric Association reviewed the evidence relating to the relative efficacy of 51 first-generation antipsychotics (FGAs) and 11 second-generation antipsychotics (SGAs) and concluded that, if differences in extrapyramidal side-effects (EPS) could be minimised (by careful dosing) and anticholinergic use avoided, there is no convincing evidence to support any advantage of SGAs over FGAs.[5] As

*The Maudsley Prescribing Guidelines in Psychiatry*, Eleventh Edition. David Taylor, Carol Paton and Shitij Kapur.

a class, SGAs may have a lower propensity for EPS and tardive dyskinesia[6] but this is somewhat offset by a higher propensity for metabolic side-effects.

When individual non-clozapine SGAs are compared with each other, it would appear that olanzapine is more effective than aripiprazole, risperidone, quetiapine and ziprasidone, and that risperidone has the edge over quetiapine and ziprasidone.[7] FGA-controlled trials also suggest an advantage for olanzapine, risperidone and amisulpride over older drugs.[8,9] The magnitude of these differences is small and must be weighed against the very different side-effect profiles associated with individual antipsychotics.

Both FGAs and SGAs are associated with a number of adverse effects. These include weight gain, dyslipidaemia, hyperprolactinaemia, sexual dysfunction, EPS, anticholinergic effects, venous thromboembolism (VTE),[10] sedation and postural hypotension. The exact profile is drug specific (see individual sections on adverse effects), although comparative data are not robust.[11] Side-effects are a common reason for treatment discontinuation.[12] Patients do not always spontaneously report side-effects, however,[13] and psychiatrists' views of the prevalence and importance of adverse effects differ markedly from patient experience.[14] 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)[15] or the Liverpool University Neuroleptic Side-Effect Ratings Scale (LUNSERS)[16] can be a useful first step in this process.

Non-adherence to antipsychotic treatment is common, which makes the guaranteed medication delivery associated with depot preparations potentially advantageous.[17] In comparison with oral antipsychotics, there is a strong suggestion that depots may be associated with better global outcome[18] and a reduced risk of rehospitalisation.[19–21]

In patients whose symptoms have not responded adequately to sequential trials of two or more antipsychotic drugs, clozapine is the most effective treatment[22–24] and its use in these circumstances is recommended by NICE.[2] The biological basis for the superior efficacy of clozapine is uncertain.[25] Olanzapine should probably be one of the two drugs used before clozapine.[7,26]



## References


1. National Institute for Health and Clinical Excellence. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. Clinical Guidance CG76. 2009. www.nice.org.uk/.
2. National Institute for Health and Clinical Excellence. Schizophrenia: core interventions in the treatment and management of schizophrenia in adults in primary and secondary care (update). Clinical Guidance 82. 2009. www.nice.org.uk/.
3. Lieberman JA et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; **353**:1209–1223.
4. Jones PB et al. Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry 2006; **63**:1079–1087.
5. Tandon R et al. World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. Schizophr Res 2008; **100**:20–38.
6. Tarsy D et al. Epidemiology of tardive dyskinesia before and during the era of modern antipsychotic drugs. Handb Clin Neurol 2011; **100**:601–616.
7. Leucht S et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. Am J Psychiatry 2009; **166**:152–163.

8. Davis JM et al. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 2003; **60**:553–564.
9. Leucht S et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009; **373**:31–41.
10. Parker C et al. Antipsychotic drugs and risk of venous thromboembolism: nested case-control study. BMJ 2010; **341**:c4245.
11. Pope A et al. Assessment of adverse effects in clinical studies of antipsychotic medication: survey of methods used. Br J Psychiatry 2010; **197**:67–72.
12. Falkai P. Limitations of current therapies: why do patients switch therapies? Eur Neuropsychopharmacol 2008; **18**(Suppl 3):S135–S139.
13. Yusufi B et al. Prevalence and nature of side effects during clozapine maintenance treatment and the relationship with clozapine dose and plasma concentration. Int Clin Psychopharmacol 2007; **22**:238–243.
14. Day JC et al. A comparison of patients' and prescribers' beliefs about neuroleptic side-effects: prevalence, distress and causation. Acta Psychiatr Scand 1998; **97**:93–97.
15. Waddell L et al. A new self-rating scale for detecting atypical or second-generation antipsychotic side effects. J Psychopharmacol 2008; **22**:238–243.
16. Day JC et al. A self-rating scale for measuring neuroleptic side-effects. Validation in a group of schizophrenic patients. Br J Psychiatry 1995; **166**:650–653.
17. Zhu B et al. Time to discontinuation of depot and oral first-generation antipsychotics in the usual care of schizophrenia. Psychiatr Serv 2008; **59**:315–317.
18. Adams CE et al. Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. Br J Psychiatry 2001; **179**:290–299.
19. Schooler NR. Relapse and rehospitalization: comparing oral and depot antipsychotics. J Clin Psychiatry 2003; **64**(Suppl 16):14–17.
20. Tiihonen J et al. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. BMJ 2006; **333**:224.
21. Leucht C et al. Oral versus depot antipsychotic drugs for schizophrenia – a critical systematic review and meta-analysis of randomised long-term trials. Schizophr Res 2011; **127**:83–92.
22. Kane J et al. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988; **45**:789–796.
23. McEvoy JP et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry 2006; **163**:600–610.
24. Lewis SW et al. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophr Bull 2006; **32**:715–723.
25. Stone JM et al. Review: the biological basis of antipsychotic response in schizophrenia. J Psychopharmacol 2010; **24**:953–964.
26. Agid O et al. An algorithm-based approach to first-episode schizophrenia: response rates over 3 prospective antipsychotic trials with a retrospective data analysis. J Clin Psychiatry 2011; **72**(11):1439–1444.



## Antipsychotic drugs: equivalent doses

Antipsychotic drugs vary greatly in potency (not the same as efficacy) and this is usually expressed as differences in 'neuroleptic' or 'chlorpromazine' 'equivalents'. Some of the estimates relating to neuroleptic equivalents are based on early dopamine binding studies and some largely on clinical experience or even inspired guesswork. *British National Formulary (BNF)* maximum doses for antipsychotic drugs bear little relationship to their 'neuroleptic equivalents'. Table 2.1 gives some approximate equivalent doses for conventional drugs.[1,2] Values given should be seen as a rough guide when transferring from one conventional drug to another. An early review of progress is essential.

It is inappropriate to convert second-generation antipsychotic doses into 'equivalents' since the dose–response relationship is usually well defined for these drugs. Dosage guidelines are discussed under each individual drug. Those readers desperate to find chlorpromazine equivalents for the newer drugs are directed to the published articles listing such data.[3,4]

**Table 2.1** Equivalent doses of conventional antipsychotic drugs

| Antipsychotic | Equivalent dose (consensus) | Range of values in literature |
|---|---|---|
| Chlorpromazine | 100 mg/day | – |
| Flupentixol | 3 mg/day | 2–3 mg/day |
| Flupentixol depot | 10 mg/week | 10–20 mg/week |
| Fluphenazine | 2 mg/day | 2–5 mg/day |
| Fluphenazine depot | 5 mg/week | 1–12.5 mg/week |
| Haloperidol | 3 mg/day | 1.5–5 mg/day |
| Haloperidol depot | 15 mg/week | 5–25 mg/week |
| Perphenazine | 10 mg/day | 10 mg/day |
| Pimozide | 2 mg/day | 2 mg/day |
| Pipotiazine depot | 10 mg/week | 10–12.5 mg/week |
| Sulpiride | 200 mg/day | 200–270 mg/day |
| Trifluoperazine | 5 mg/day | 2.5–5 mg/day |
| Zuclopenthixol | 25 mg/day | 25–60 mg/day |
| Zuclopenthixol depot | 100 mg/week | 40–100 mg/week |



## References

1. Foster P. Neuroleptic equivalence. Pharm J 1989; **243**:431–432.
2. Atkins M, Burgess A, Bottomley C, Riccio M. Chlorpromazine equivalents: a consensus of opinion for both clinical and research implications. Psychiatr Bull 1997; **21**:224–226.
3. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry 2003; **64**:663–667.
4. Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. International consensus study of antipsychotic dosing. Am J Psychiatry 2010; **167**:686–693.

## Antipsychotic drugs: minimum effective doses

Table 2.2 suggests the minimum dose of antipsychotic likely to be effective in schizophrenia (first episode or relapse). At least some 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 (as have standard texts such as the *BNF* and Summaries of Product Characteristics). Only oral treatment with commonly used drugs is covered.