

The Maudsley

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# Prescribing Guidelines in Psychiatry

ELEVENTH EDITION

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 WILEY-BLACKWELL

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# The Maudsley Prescribing Guidelines in Psychiatry

11th Edition

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# ***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

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*David Taylor*

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# ***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***

<b>ACE</b>	angiotensin-converting enzyme
<b>ACh</b>	acetylcholine
<b>AChE</b>	acetylcholinesterase
<b>AD</b>	Alzheimer's disease
<b>ADAS-cog</b>	Alzheimer's Disease Assessment Scale - cognitive subscale
<b>ADH</b>	alcohol dehydrogenase/antidiuretic hormone
<b>ADHD</b>	attention deficit hyperactivity disorder
<b>ADL</b>	Activities of Daily Living
<b>ADR</b>	adverse drug reaction
<b>ALT</b>	alanine aminotransferase
<b>ASD</b>	autism spectrum disorders
<b>AST</b>	aspartate aminotransferase
<b>BAD</b>	bipolar affective disorder
<b>BAP</b>	British Association for Psychopharmacology
<b>BDNF</b>	brain-derived neurotrophic factor
<b>BMI</b>	Body Mass Index
<b>BNF</b>	<i>British National Formulary</i>
<b>BP</b>	blood pressure
<b>BPD</b>	borderline personality disorder
<b>bpm</b>	beats per minute
<b>BuChE</b>	butyrylcholinesterase
<b>CBT</b>	cognitive behaviour therapy
<b>CI</b>	confidence interval
<b>CIWA-Ar</b>	Clinical Institute Withdrawal Assessment of Alcohol Scale Revised
<b>CK</b>	creatine kinase
<b>CNS</b>	central nervous system
<b>COMT</b>	catechol- <i>O</i> -methyltransferase
<b>COX</b>	cyclo-oxygenase
<b>CSM</b>	Committee on Safety of Medicines
<b>CYP</b>	cytochrome P450
<b>DAI</b>	Drug Attitude Inventory
<b>DHA</b>	docosahexanoic acid
<b>DHEA</b>	dehydroepiandrosterone

<b>DLB</b>	dementia with Lewy bodies
<b>DSM</b>	<i>Diagnostic and Statistical Manual of Mental Disorders</i>
<b>DT</b>	delirium tremens
<b>DVLA</b>	Driver and Vehicle Licensing Agency
<b>ECG</b>	electrocardiogram
<b>ECT</b>	electroconvulsive treatment
<b>EEG</b>	electroencephalogram
<b>eGFR</b>	estimated GFR
<b>EPA</b>	eicosapentanoic acid
<b>EPS</b>	extrapyramidal side-effects
<b>ERK</b>	extracellular signal-regulated kinase
<b>FBC</b>	full blood count
<b>FDA</b>	Food and Drug Administration
<b>FGA</b>	first-generation antipsychotic
<b>FPG</b>	fasting plasma glucose
<b>FTI</b>	Fatal Toxicity Index
<b>GABA</b>	$\gamma$ -aminobutyric acid
<b>GAD</b>	generalised anxiety disorder
<b>GASS</b>	Glasgow Antipsychotic Side-effect Scale
<b>GBL</b>	$\gamma$ -butyryl-lactone
<b>G-CSF</b>	granulocyte-colony stimulating factor
<b>GFR</b>	glomerular filtration rate
<b>GGT</b>	$\gamma$ -glutamyl transferase
<b>GHB</b>	$\gamma$ -hydroxybutyrate
<b>GI</b>	gastrointestinal
<b>GIT</b>	gastrointestinal tract
<b>GM-CSF</b>	granulocyte macrophage colony-stimulating factor
<b>HDL</b>	high-density lipoprotein
<b>HR</b>	hazard ratio
<b>ICD</b>	<i>International Classification of Diseases</i>
<b>IM</b>	intramuscular
<b>INR</b>	international normalised ratio
<b>IV</b>	intravenous
<b>LAI</b>	long-acting injection
<b>LD</b>	learning disability

<b>LDL</b>	low-density lipoprotein
<b>LFT</b>	liver function test
<b>LUNSERS</b>	Liverpool University Neuroleptic Side-Effect Ratings Scale
<b>MAO-A</b>	monoamine oxidase A
<b>MAOI</b>	monoamine oxidase inhibitor
<b>MCI</b>	mild cognitive impairment
<b>MHRA</b>	Medicines and Healthcare products Regulatory Agency
<b>MI</b>	myocardial infarction
<b>MMSE</b>	Mini Mental State Examination
<b>NICE</b>	National Institute for Health and Clinical Excellence
<b>NMDA</b>	N-methyl-D-aspartate
<b>NMS</b>	neuroleptic malignant syndrome
<b>NNT</b>	number needed to treat
<b>NRT</b>	nicotine replacement therapy
<b>NSAID</b>	non-steroidal anti-inflammatory drug
<b>OCD</b>	obsessive compulsive disorder
<b>OGTT</b>	oral glucose tolerance test
<b>PANDAS</b>	Paediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus
<b>PDD-NOS</b>	pervasive developmental disorders-not otherwise specified
<b>PEG</b>	percutaneous endoscopic gastrostomy
<b>POMH-UK</b>	Prescribing Observatory for Mental Health - UK
<b>prn</b>	<i>pro re nata</i>
<b>PTSD</b>	post-traumatic stress disorder
<b>PUFA</b>	polyunsaturated fatty acid
<b>RCT</b>	randomised controlled trial
<b>RLAI</b>	risperidone long-acting injection
<b>RRBI</b>	restricted repetitive behaviours and interests
<b>SADQ</b>	Severity of Alcohol Dependence Questionnaire
<b>SAWS</b>	Short Alcohol Withdrawal Scale
<b>SGA</b>	second-generation antipsychotic
<b>SIADH</b>	syndrome of inappropriate secretion of antidiuretic hormone
<b>SJW</b>	St John's wort
<b>SPC</b>	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.<sup>1</sup> 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 (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 <sup>2,3</sup>	>7 mg/l bipolar disorder	Trough	2 weeks	Induces its own metabolism. Time to steady state dependent on autoinduction
Clozapine	350–500 µg/l Upper limit of target range is ill defined	Trough (12 h post-dose if once daily)	2–3 days	See text
Lamotrigine <sup>4-7</sup>	Not established but suggest 2.5–15 mg/l	Trough	5 days 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 <sup>8-11</sup>	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 <sup>12</sup>	20–60 µg/l (9-OH risperidone)	Trough	2–3 days oral 2 months depot	No obvious reason to suspect range should be any different from risperidone. Some practical confirmation
Phenytoin <sup>3</sup>	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

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 <sup>13</sup>	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 <sup>2,3,14–17</sup>	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<sup>18–20</sup> and older patients<sup>18,20</sup> 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;<sup>21</sup> mean levels of 367 µg/l<sup>20</sup> 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,<sup>18</sup> 377 µg/l<sup>21</sup> and 395 µg/l.<sup>19</sup> A plasma level threshold of below 320 µg/l has been found to predict avoidance of EPS.<sup>21</sup> A review of the current literature<sup>22</sup> 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<sub>2</sub> dopamine occupancy seen at doses above approximately 10 mg/day.<sup>23</sup> 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.<sup>24</sup> Target plasma level ranges for optimal clinical response have been suggested as 146–254 µg/l<sup>25</sup> and 150–300 µg/l,<sup>26</sup> with adverse effects observed above 210 µg/l.<sup>26</sup> Interindividual variation in aripiprazole plasma levels has been observed but not fully investigated, although gender appears to have little influence.<sup>27,28</sup> Age, metabolic enzyme genotype and interacting medications seem likely causes of variation<sup>26-29</sup> 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**<sup>24</sup> 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.