The Maudsley

THE SOUTH LONDON AND MAUDSLEY NHS FOUNDATION TRUST
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Prescribing Guidelines in Psychiatry

ELEVENTH 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

maintains a growing database of over 15,000 scientific references essential for the production of *The Guidelines*.

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

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 (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 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 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 (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[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

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.