FUNDAMENTALS OF CLINICAL PSYCHOPHARMACOLOGY

FOURTH EDITION

EDITED BY
IAN M ANDERSON
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British Association for Psychopharmacology

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Fourth Edition

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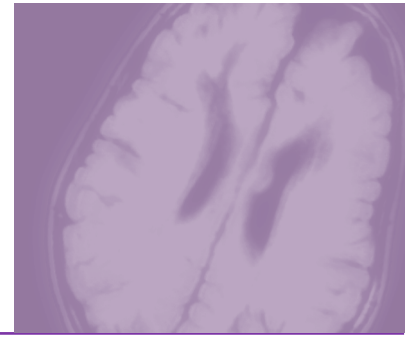

This book is dedicated to the memory of Ian Reid who died prematurely in 2014 after a short illness. He was co-editor of the first three editions of *Fundamentals* and a contributor to a number of chapters. Without him the earlier editions, and therefore this one, would not have been published. Ian was proud to have been one of the first to propose the neurotrophic and neuroplasticity hypothesis of antidepressant action and was well known for his fierce intelligence, wit and iconoclasm. You can read more about Ian in the BAP December 2014 newsletter (http://www.bap.org.uk/pdfs/BAPNewsletterDec2014.pdf). He is greatly missed on both a professional and a personal level.

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Foreword

It is a pleasure to write the foreword to this welcome, and much anticipated, new edition of *Fundamentals*. The book is a key component of the British Association for Psychopharmacology (BAP)'s commitment to ensuring that accurate, evidence-based and unbiased information about psychopharmacology is available to a wide audience through a variety of activities and media. True to the BAP ethos, the book spans the range of the discipline, from the mode of action and side effects of drugs, via key aspects of the biology of psychiatric disorders, to meta-analyses of clinical trials. Wherever possible, it is anchored to the practice guidelines produced by the UK National Institute for Health and Care Excellence (NICE) and the BAP itself. The editors and authors are to be commended for bringing together such a comprehensive and up-to-date book that will be of particular use to trainees and consultant psychiatrists, as well as to other mental health professionals and physicians, both in their day-to-day practice and as an accessible and concise reference volume. I also echo the authors' dedication and gratitude to the late Ian Reid for his critical role in co-editing and contributing to the earlier editions.

There is no other area of medicine where a book such as this, summarising the science behind, and the practice of, therapeutic prescribing could be seen as anything other than of value and importance. Yet there is a continuing view held by a vociferous minority that the drugs used in psychiatry are at best ineffective, at worst dangerous, and that their use is usually, if not always, inappropriate. Moreover, those who carry out research in, or are supportive of, psychopharmacology, are often portrayed as being in the pocket of the pharmaceutical industry. Any rational reading of the current text, or perusal of the author list, shows that such views are unsustainable and unfair. Yet the criticisms do highlight the need for all of us who advocate that medication has an important place in the treatment of people with mental health disorders, to ensure that our actions and opinions are justified, and with transparency regarding any real or perceived conflicts of

interest. Certainly, it is crucial that anyone prescribing psychotropic medication does so with a solid grounding in the underlying science and clinical evidence, and that they present the case for, and against, medication in a balanced fashion to patients[1]. But these principles apply equally to those studying or advocating psychological or other interventions; these are also susceptible to bias, error and conflicts – albeit often overlooked and less clearly delineated[2].

The real argument in favour of psychopharmacology is, however, that drugs work, and with effect sizes comparable to those in general medicine[3]. Nor should we be defensive about comparisons with psychological treatment[4]. For example, using like-for-like methodology, antidepressants have at least comparable clinical benefit to psychological treatments for depression, even after taking into account unpublished drug studies[5,6]. In the acute treatment of schizophrenia, drug treatments have moderate-to-large effects, whereas an addition of cognitive therapy adds only a small-to-moderate benefit, which is lower in the more methodologically rigorous studies[7,8]. In essence, whether one views the psychopharmacological glass as half full or half empty, an equally critical conclusion should be drawn with regard to psychotherapies.

None of these points are intended to downplay the place of psychological treatments in psychiatry – they work too and are often preferred by patients – but rather to highlight that all patients deserve clear and accurate advice about, and access to, effective psychopharmacological *and* psychological treatments. In this context, the new edition of *Fundamentals* provides a balanced and valuable summary of the evidence for the efficacy, indications and mechanisms of action of current psychotropic drugs. It will be of wide clinical value, as well as provide a clear synthesis of the psychopharmacological evidence, and a defence against misplaced or unfounded criticisms.

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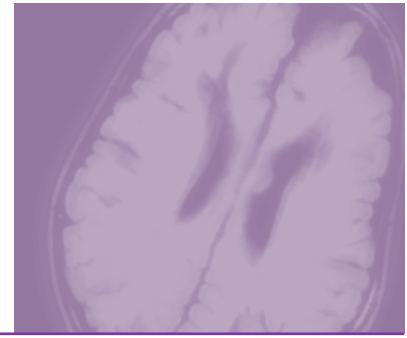

Preface

It is 13 years since the first edition of *Fundamentals of Clinical Psychopharmacology* was published in 2002. It was intended to be a frequently updated, affordable, concise and practical textbook that would meet the needs of trainees and practitioners seeking to keep abreast of the state of the art of psychopharmacology. After further editions in 2004 and 2006, why has there been a gap of nine years before this edition? The reasons have included a slowdown in drug development, translating into fewer clinically available new drugs, the financial and marketing environment (especially since 2008) and some revision fatigue on the part of editors and authors. We are therefore grateful to the publisher for wishing to undertake this new edition and for being willing to make it more affordable and therefore hopefully accessible to a wider audience, particularly trainees. We are also extremely grateful to the authors – both past and new contributors – for agreeing to provide their time and expertise. The *Fundamentals* developed from the British Association for Psychopharmacology (BAP)'s 'Psychopharmacology Course for Psychiatrists in Training', which has developed into the acclaimed current 'Masterclasses in Clinical Psychopharmacology' for all clinicians involved in prescribing. This book is part of the strong educational tradition of the BAP (see later for more details).

The remit of the book is to provide a core of up-to-date, clinically relevant information about drugs in the context of current knowledge about the biological basis of the disorders they treat. For this new edition, we have updated all the chapters and have included a new one on practical prescribing. It has allowed us to correct inevitable mistakes and we continue to put drug prescribing into the context of National Institute of Health and Care Excellence (NICE) guidance. As well as having obvious UK relevance, NICE remains the most influential, comprehensive and coherent authority producing evidence-based guidance across the world. However, guidance is increasingly being interpreted in a narrow way and can be employed as a restriction on choice rather than as an enabler of good practice. It is therefore

vital to critically evaluate the evidence and at times adopt a healthy scepticism of guidelines, because of the complex procedures, and often political compromises, that lie behind them. As with previous editions, for ease of reading, we have not included in-text citations. Key references, including any clinical studies mentioned, are given at the end of each chapter together with additional further reading.

The current contributors to the book are leading psychopharmacologists, predominantly from the United Kingdom, but the content of the book has developed over subsequent editions and we must thank the many others who have been involved in the material over the years, and they are listed in the acknowledgements. We would particularly like to acknowledge the contribution of Prof Ian Reid, to whom this book is dedicated.

The BAP was founded in 1974, with the general intention of bringing together those from clinical and experimental disciplines, human- and animal-based research as well as members of the pharmaceutical industry involved in the study of psychopharmacology. It is one of the largest national associations of its kind in the world. The BAP arranges scientific meetings, fosters research and teaching, encourages the publication of research, produces clinical guidelines, publishes the *Journal of Psychopharmacology* and provides guidance and information to the public on matters relevant to psychopharmacology. BAP evidence-based guidelines are available for downloading for personal use from our website. The BAP has also produced an online continuing professional development (CPD) resource, which is frequently updated and expanded. This, together with the various face-to-face meetings organised by the BAP, is recommended to anyone wanting to gain further information beyond this book.

Membership of the BAP is open to anyone with a relevant degree related to neuroscience, including clinical medical, nursing, or pharmacy degrees. If you are interested in any aspect of psychopharmacology, we would strongly encourage you to consider joining. You can find out more on our website: http://www.bap.org.uk.

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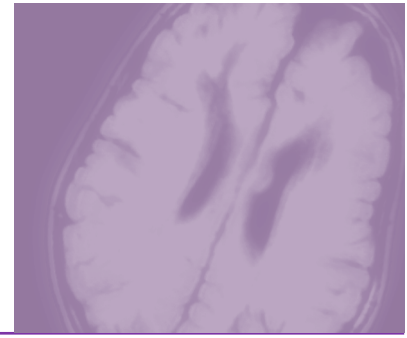
Prof Anderson founded the Specialist Service for Affective Disorders in Manchester and was director until 2011. His research interests include the aetiology and treatment of mood disorders, the mechanism of action of antidepressants and evidence-based psychiatry. He chaired the guideline development group for the 2009 update of the NICE depression clinical guideline and is an author on several consensus treatment guidelines from the British Association for Psychopharmacology (BAP). He is a past general secretary of the BAP.

Dr R Hamish McAllister-Williams, BSc, MBChB, PhD, MD, FRCPsych, is reader in clinical psychopharmacology, Institute of Neuroscience, Newcastle University, and honorary consultant psychiatrist, Regional Affective Disorders Service, Northumberland Tyne and Wear NHS Foundation Trust.

Dr McAllister-Williams is the lead consultant in the tertiary level Regional Affective Disorders Service based in Newcastle for patients with treatment-refractory mood disorders. His research focuses on the pathophysiology and treatment of both bipolar and unipolar affective disorders, and he is an author of the BAP consensus guidelines for treating depression. He is a past general secretary of the BAP and was appointed its director of education in 2012.



A note on nomenclature

The current classification, or nomenclature, of psychotropic drugs can be unhelpful in understanding their pharmacology or clinical use. In clinical use, it has grown in a random way with inconsistencies in whether drugs are classified according to chemical structure, history, clinical effects or pharmacology. The World Health Organisation (WHO) system, the Anatomical Therapeutic Chemical Classification System (http://www.who.int/classifications/atcddd/en/), is a little better, with the division of drugs into different groups according to the organ or system on which they act and their chemical, pharmacological, and therapeutic properties. For example, antipsychotics are classified according to chemical structure but antidepressants according to pharmacology. Many drugs are listed under an 'other' category, and this can be a particular problem with newer compounds. In addition, drugs which act on a range of disorders sit uneasily in the current schemes (e.g. 'antidepressants' are also first-line drugs in treating anxiety disorders, and newer 'antipsychotics' are effective treatments for depression).

In response to this, a taskforce, supported by four major neuropsychopharmacology organisations, has proposed a multi-axial, pharmacologically driven nomenclature for psychiatric drugs (neuroscience-based nomenclature or 'NbNomenclature') that they have field-tested (http://www.ecnp.eu/projects-initiatives/nomenclature.aspx). The final published version has four axes. Axis 1 identifies the primary pharmacological target and mode of action, Axis 2 the approved indications, Axis 3 efficacy and side effects and Axis 4 human and animal neurobiology. NbNomenclature is available as a free downloadable app for Android phones and iPhones/iPads.

Although there is dissatisfaction with the current nomenclature, and a wish to apply pharmacological knowledge to clinical use of drugs, it remains to be seen whether this new system will pass into general use. Given that we still lack sufficient knowledge of the key mechanism/s of action of drugs used in psychiatry, and how their pharmacology relates to

clinical action, the Axis 1 classification has to be viewed as provisional. In addition, the multi-axial system is somewhat cumbersome for clinical use. We have therefore decided not to adopt the NbNomenclature system for this book. For ease of use, we have retained the (admittedly imperfect) historic clinically based groupings of drugs, but detail their currently known pharmacology.

Ian M Anderson
R Hamish McAllister-Williams

List of abbreviations

1-PP	1-(2-Pyrimidinyl)piperazine
2-AG	2-Arachidonylglycerol
5-HT	5-Hydroxytryptamine, serotonin
5-HTP	5-Hydroxytryptophan
5-HTPDC	5-HTP decarboxylase
5-HIAA	5-Hydroxyindoleacetic acid
5-HTT	5-HT transporter
5-HTTLPR	Serotonin transporter linked promoter polymorphism
AC	Adenylate cyclase
ACE	Angiotensin-converting enzyme
ACh	Acetylcholine
AChE	Acetylcholinesterase
AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale-cognitive subscale
ADH	Antidiuretic hormone
ADHD	Attention deficit/hyperactivity disorder
ADL	Activities of daily living
ALDH	Aldehyde dehydrogenase
AMP	Adenosine monophosphate
AMPA	Amino-3-hydroxy-5-methyl-isoxazole propionate
AMTS	Abbreviated Mental Test Score
AP5	2-Amino-5-phosphopentanoic acid
ApoE	Apolipoprotein E
APP	Amyloid precursor protein
ASD	Autism spectrum disorder
ATP	Adenosine triphosphate
ATPase	Adenosine triphosphatase
AUC	Area under the curve

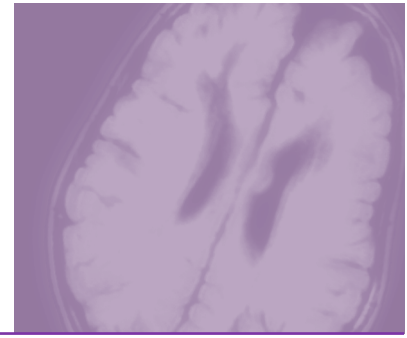
β-CCE	Ethyl-β-carboline-3-carboxylate
BD	Bipolar disorder
BDI	Beck Depression Inventory
BDNF	Brain-derived neurotrophic factor
BDZ	Benzodiazepine
BEHAVE-AD	Behavioural Pathology in Alzheimer's Disease scale
BNF	British National Formulary
BPSD	Behavioural and psychiatric symptoms of dementia
Ca^{2+}	Calcium
cAMP	Cyclic adenosine monophosphate, cyclic AMP
CB	Cannabinoid
CBT	Cognitive behavioural therapy
CCK	Cholecystokinin
CCK4	Cholecystokinin tetrapeptide
CDR	Clinical Dementia Rating
ChAT	Choline acetyltransferase
CIBIC	Clinician Interview Based Impression of Change
Cl^-	Chloride
C_{max}	Maximum plasma concentration (pharmacokinetics)
CNS	Central nervous system
CO_2	Carbon dioxide
CoA	Coenzyme-A
COMT	Catechol-O-methyltransferase
COX-2	Cyclooxygenase-2
C_p	Plasma concentration (pharmacokinetics)
CRE	cAMP response elements
CREB	cAMP response element binding protein
CRF	Corticotrophin-releasing factor
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CYP/CYP450	Cytochrome P450
D	Dopamine (used for receptor terminology)
DA	Dopamine
DAG	Diacylglycerol
DAT	Dopamine transporter
DβH	Dopamine-β-hydroxlase
DOPA	Dihydroxyphenylalanine
DOPAC	Dihydroxyphenylacetic acid
DOPADC	DOPA decarboxylase
DSM-IV/5	Fourth/fifth revision of the *Diagnostic and Statistical Manual of Mental Disease* (American Psychiatric Association)
EAAT	Excitatory amino acid transporters
ECG	Electrocardiogram

ECT	Electroconvulsive therapy
EEG	Electroencephalogram
EPSE	Extrapyramidal side effects
EU	European Union
FBC	Full blood count
FDA	Food and Drugs Administration (United States regulator)
FMO	Flavin-containing monooxygenase
G	Guanine nucleotide
GABA	γ (gamma) aminobutyric acid
GAD	Generalised anxiety disorder, glutamic acid decarboxylase
GBL	Gamma-butyrolactone
GCP	Good clinical practice
GDP	Guanosine diphosphate
GFR	Glomerular filtration rate
GHB	Gamma-hydroxybutyrate
GI	Gastrointestinal
G_i	Inhibitory G-protein
GIRK	G-protein-linked inward rectifying potassium channel
GluT	Glutamate transporter
GlyT	Glycine transporter
GPCR	G-protein-coupled receptor
G_s	Stimulatory G-protein
GTP	Guanosine triphosphate
GTPase	Guanosine triphosphatase
GSK-3β	Glycogen synthase kinase 3 beta
H	Histamine
HERG	Human ether-a-go-go (gene)
HLA	Human leucocyte antigen
HPA	Hypothalmic—pituitary—adrenal
HRT	Hormone replacement therapy
HVA	Homovanillic acid
IADL	Instrumental Activities of Daily Living
ICD-10	Tenth revision of the *International Classification of Diseases* (World Health Organisation)
IDDD	Interview for Deterioration in Daily Living in Dementia
I_{Kr}	Delayed rectifier K^+ channel
IL-6	Interleukin-6
im	Intramuscular
IP_3	Inositol trisphosphate
IPT	Interpersonal therapy
ITT	Intention to treat
iv	Intravenous
K^+	Potassium

LAAM	Levo-alpha-acetylmethadol
LAT1	L-type amino acid transporter 1
LC	Locus coeruleus
L-DOPA	L-dihydroxyphenylanine
LFTs	Liver function tests
LOCF	Last observation carried forward
LSD	Lysergic acid diethylamide
LTA	Lateral tegmental area
LTP	Long-term potentiation
mACh(R)	Muscarinic acetylcholine (receptor)
MAO	Monoamine oxidase
MAOI	Monoamine oxidase inhibitor
MAPK	Mitogen-activated protein kinase
MDA	Methylenedioxyamfetamine/ methylenedioxyamphetamine
MDD	Major depressive disorder
MDEA	Methylenedioxyethylamfetamine/ methylenedioxyethylamphetamine
MDMA	Methylenedioxymethamfetamine/ methylenedioxymethamphetamine
MDPV	3,4-Methylenedioxypyrovalerone
MEMO	Medicines Monitoring (Unit)
Mg^{2+}	Magnesium
mGLuR	Metabotropic glutamate receptor
MHPG	3-Methoxy-4-hydroxyphenylglycol
MHRA	Medicines and Healthcare Products Regulatory Authority (United Kingdom)
MK-801	Dizocilpine
MMRM	Mixed effects model repeated measures
MMSE	Mini-Mental State Examination
MPAC	Metal protein attenuating compound
M-PEM	Modified prescription event monitoring
MT	Methoxytyramine, melatonin
MTA	Multimodal Treatment Study of ADHD
NA	Noradrenaline (norepinephrine)
Na^{+}	Sodium
nACh(R)	Nicotinic acetylcholine (receptor)
NARI	Noradrenaline reuptake inhibitor
NaSSa	Noradrenaline- and serotonin-specific antidepressant
NAT	Noradrenaline transporter
NICE	National Institute for Health and Care Excellence (United Kingdom)
NK	Neurokinin
NM	Normetanephrine

NMDA	*N*-methyl D-aspartate
NMS	Neuroleptic malignant syndrome
NPI	Neuropsychiatric Inventory
NPY	Neuropeptide Y
NSAID	Nonsteroidal anti-inflammatory drug
NT	Neurotensin
OCD	Obsessive-compulsive disorder
OPCS	Office of Population Censuses and Surveys
OR	Odds ratio
OX	Orexin
PAG	Periaqueductal grey
PCB	Polychlorinated biphenyl
PCP	Phencyclidine
PEM	Prescription event monitoring
PET	Positron emission tomography
PHQ-9	Patient Health Questionnaire-9
PLC	Phospholipase-C
PNMT	Phenylethanolamine-N-methyltransferase
PPARγ	Peroxisome proliferator-activated receptor gamma
PPI	Patient and public involvement
PROM	Patient reported outcome measure
PTSD	Post-traumatic stress disorder
Q	Quantity of drug (pharmacokinetics)
QTc	Interval between Q and T waves on the electrocardiogram corrected for heart rate
RCT	Randomised controlled trial
REM	Rapid eye movement
RIMA	Reversible inhibitor of monoamine oxidase-A
RTK	Receptor tyrosine kinase
SCEM	Specialised cohort event monitoring
SERT	Serotonin (5-HT) transporter
SIADH	Syndrome of inappropriate ADH secretion
SJS	Stevens–Johnson syndrome
SMARTS	Systematic Monitoring of Adverse Events Related to Treatments
SmPC	Summary of product characteristics
SNAP-25	Synaptosomal-associated protein 25
SNRI	Serotonin and noradrenaline reuptake inhibitor
SPECT	Single photon emission computerised tomography
SSRI	Selective serotonin reuptake inhibitor
SUCRA	Surface under the cumulative response curve

$t½$	Half-life (pharmacokinetics)
T3	Triiodothyronine
TCA	Tricyclic antidepressant
TH	Tyrosine hydroxylase
THA	Tacrine, tetrahydroaminoacridine
THC	δ-9-Tetrahydrocannabinol
t_{max}	Time to maximum (peak) plasma concentration
TNFα	Tumour necrosis factor-α
TPH	Tryptophan hydroxylase
TRH	Thyrotropin-releasing hormone
TRK-B	Tropomyosin receptor kinase B
TSH	Thyroid-stimulating hormone
UK	United Kingdom
US/USA	United States/United States of America
V_d	Volume of distribution (pharmacokinetics)
VGAT	Vesicular GABA transporter (also VIAAT)
VGLUT	Vesicular glutamate transporter
VIAAT	Vesicular inhibitory amino acid transporter (also VGAT)
VMAT	Vesicular monoamine transporter
VNTR	Variable number tandem repeat
VTA	Ventral tegmental area
Zn^{2+}	Zinc



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