Practical Psychopharmacology

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Translating Findings from Evidence-Based Trials into Real-World Clinical Practice

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To my wife, best friend, trusted source, and most-beloved critic Carrie; and to Joshua, Brian, Hannah, and Jonah, for their limitless support, patience, and encouragement throughout the conception, gestation, and delivery of this work.

- J.F.G.

In memory of Dr. Daniel X. Freedman, mentor, colleague, and scientific father;

to Shakila Marie

- S.M.S.

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Foreword

Over the past four decades, psychopharmacology has become a major tool in the treatment armamentarium for patients with psychiatric disorders. The early days revolved around the first-generation antipsychotics and antidepressants. Since then we have seen the introduction of a number of drugs with different mechanisms of action such that today we have many more tools in our toolbox. Still, we have many patients with so-called refractory disorders necessitating the need for even more agents with unique mechanisms of action. Such efforts offer considerable hope for both clinicians and patients alike. But as we develop new agents we need to be able to evaluate the data that have been used to support their approval. This is even more important today when we are seeing drugs approved with less than the previous standard of two positive Phase III trials. Academics and clinicians both need to have a knowledge base to assess these new data to guide their decision-making. Where are we going to get it? Now we have a textbook – *Practical Psychopharmacology* – that can help guide readers through this area and potentially other domains that affect research and treatment. The Goldberg and Stahl book is a tremendous resource for enhancing evidence-based psychopharmacologic care.

The text elegantly bridges key aspects of preclinical and clinical pharmacology, biostatistics, pharmacogenetics, and clinical practice, and this bridge will enable the reader to understand the key issues in research and drug assessment that determine whether an agent or a laboratory test is accepted into clinical practice and ultimately used in daily practice. The book consists of two major sections (General Principles and Targets of Pharmacotherapy). The first section – General Principles – contains 12 chapters that include amongst others: Targets of Treatment: Categories versus Dimensions of Psychopathology; Placebo and Nocebo Effects; Tailoring the Fit: Moderators and Mediators of Treatment Outcome; Pharmacogenetics: When Relevant, When Not, etc. The second section on Targets of Pharmacotherapy contains 10 chapters and is more traditional in coverage, including, amongst others: Disordered Mood and Affect; Psychosis; Cognition, etc.

The General Principles section is what sets this book apart. It builds the bridge from research to better practice. It elucidates issues in each of these key areas and explains them in an intelligible manner for the reader to digest. It makes it easy to understand why these areas are important for the clinician. That is no easy task and I found myself getting a super refresher course in key research areas related to psychopharmacology and learning a lot about some domains that I probably should have known more about.

Let me give some examples of key areas covered in the book. Goldberg and Stahl go beyond using simple p-values to judge efficacy and give us a precis on effect sizes. Effect sizes are measures of clinical relevance of a drug–placebo difference that are independent of the p-value and the size of the study. This book explains in an intelligible way what an effect size is, how it is determined, and the relevance to clinical effect. It then gives examples of effect sizes of known agents – e.g., memantine for depression, esketamine, etc. The reader will be somewhat surprised that agents we prescribe all the time (e.g., some antidepressants) actually exert small effects. Taken to an extreme in assessing some drugs in specific types of patients (e.g., some antidepressants in milder depressives), investigators have argued the agents are not effective. The authors review this literature in sufficient detail and in a clear manner such that the reader can then judge the clinical significance of specific clinical trials. And that is the point of this book. It gives the practitioner the information from the research literature to better select an individual treatment for a particular patient, making personalized medicine ultimately achievable.

Another example of helping to bridge from studies to practice is the chapter on mediators and moderators. This work was pioneered by my colleague at Stanford – Helena Kraemer – who developed a method of analysis that goes beyond the drug versus placebo comparison to attempt to ferret out the moderators of response to a particular agent, such as age, gender, or some other clinical or biologic feature. That helps the clinician to determine who best to treat with a particular agent. Mediators are those variables that change with a particular treatment and indicate the key parameters that are affected in the course of response, either positive or negative. For example, a change in plasma catecholamines could mediate the response to clozapine or a change in weight on an atypical might mediate developing insulin resistance or diabetes. Again,

the authors do a fine job in teaching us how to apply these types of analyses.

A third example is the development of pharmacogenetics to predict efficacy or side effects. In some ways, specific genetic variants are moderators of response. These tests have become increasingly used by clinicians, although there are a number of researchers who question their clinical utility. The authors do an excellent job explaining what a gene is, what an allele is, what SNPs are, how studies are performed, and how we should interpret results to date. The chapter is clear and reviews a number of important and potentially useful markers of both response and side effects. And there are many other examples in the remaining nine chapters in this section.

Crossing over to specific types of agents and disorders, Goldberg and Stahl place the data on specific agents in the context that they have brilliantly laid out for us in Part I on General Principles. We now see what the issues are with the available agents and those being developed that will inform practice today and for the future. This is a book that is worth owning by any practitioner or student of clinical psychopharmacology. Kudos to Goldberg and Stahl for enhancing the literature in this important area.

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Preface

The impetus for this book comes from our perception of a distinct unmet need in the world of clinical psychopharmacology, that of a marriage between clinical neuroscience and evidence-based trials, brokered by the matchmaker of pragmatism. There is, on the one hand, an ever-growing literature of randomized controlled trials, crossover trials, open case series, proof-of-concept studies, and case reports that lend varying degrees of support for innovative therapeutic strategies; on the other hand, there exists a clinical reality in which patients frequently start and stop drugs not always for compelling reasons, where everyday practitioners manage patients on extensive polypharmacy regimens that may at times look like random assemblages, pharmacodynamic rationales are not always purposeful, mechanisms of action can be unwittingly redundant or contradictory, and ineffective treatments may senselessly get retained (sometimes perhaps even hoarded) rather than deprescribed.

Simultaneously, there is often a mismatch between the crisp diagnostic entities enrolled in industry-based large-scale randomized trials and the often more ill-defined patient presentations that many clinicians encounter in more real-life, nonspecialized treatment settings. While clinical trialists agonize over whether each and every prospective research subject fully meets DSM-5 or ICD-10 diagnostic symptom and duration criteria based on a detailed structured clinical interview – often having to account for the presence of many co-occurring disorders – real-world practitioners generally lack the time, resources, and often the training to apply rigorous diagnostic criteria to rule in or rule out well-defined categorical disorders.

To make matters murkier, the National Institute of Mental Health (NIMH) opted in 2013 to discard DSM-5 diagnostic categories and their inclusion or exclusion criteria altogether, instead favoring a more dimensional than categorical framework meant to reflect suspected underlying neurobiological processes. Making "accurate" diagnoses has never been harder, as the field evolves in its thinking about what constitutes a true clinical entity and its consequent targets of therapy. In a kind of weird parallel process, the traditional nomenclature for classifying psychotropic drugs has come under greater criticism based on outcomes from both controlled and observational treatment studies (such as STAR*D and CATIE), and evolving hypotheses about disease processes and drug mechanisms that render simplistic theories about neurotransmitter "imbalances" archaic and obsolete. Drugs once called antidepressants seem not to treat depression in reliable and robust ways, drugs called antipsychotics treat more than psychosis, certain blood pressure drugs have found new life treating symptoms of anxiety and posttraumatic stress disorder, and (at least some) anticonvulsants possess varied psychotropic properties unrelated to their antiseizure efficacy. New psychotropic properties are being recognized in old drugs (such as prazosin, ketamine, isradipine, scopolamine, anti-inflammatories, and immunomodulators), while novel therapeutics have prompted growing interest in new potential mechanisms of action (such as opioid receptor modulation for depression (e.g., buprenorphine), $5HT_{2A}$ blockade for psychosis (e.g., pimavanserin), GABA modulation and second-generation neurosteroids for postpartum depression (e.g., brexanolone), and VMAT2 inhibition for movement disorders (e.g., valbenazine, deutetrabenazine), among other innovative treatment strategies.

Busy practitioners often find it hard to stay current with the literature. They may be less familiar with the data to support or refute particular drug choices in particular settings, and they may choose medications for their intended or hoped-for effects on specific symptoms (such as inattention, or impulsive aggression, or anxiety, or insomnia) rather than on coherent constellations of signs and symptoms that form a recognizably distinct entity. When clinical presentations are diagnostically ambiguous, there is often the urge to shoe-horn or force-fit an overarching (and reimbursable) diagnostic label upon patients whose problems may simply not be well captured by existing nomenclature. Meanwhile, clinical neuroscientists concern themselves with putative mechanisms of drug action, brain circuitry relevant to clinical phenotypes, and possible pharmacogenetic considerations that might one day meaningfully help to refine precision medicine on a case-by-case basis.

This book seeks to bridge the many gaps that now exist between the activities of everyday clinical practice and findings from evidence-based trials, between the language of neuropharmacology and the language of symptom-targeted interventions, between systematic approaches to iterative, synergistic pharmacotherapies and the accrual

of irrational, overextensive polypharmacies. Throughout the pages ahead, our aim is to articulate a scientifically informed approach to clinical psychopharmacology, distilling generalizable information from clinical trials in ways that might help the extrapolation process from the clinical trials database to everyday practice. In a way, this conceptual merger invites the practitioner to assume the role of clinical trialist, viewing every patient as a subject for whom target symptoms are objectified, outcomes are tracked, and rationales form the basis for decision-making about drug therapies.

We also hope to reorient the clinician's attention *away* from the scienceless concept of whether or not a drug is FDA-approved for a particular condition as an organizing principle for pharmacological decision-making. While the drug regulatory approval process provides a public service for quality assurance of drug manufacturing and safety, it is fundamentally an enterprise driven more by commercial interests than neuroscience. At best, it applies neuroscientific concepts for the purposes of substantiating a pharmacodynamic or pharmacokinetic claim for the relevance of a given compound for a particular use. Regulatory approval means that pharmaceutical manufacturers have legal permission to advertise a proprietary compound; it is not built around advancing knowledge for the sake of knowledge about how the brain works. Plenty of generic, nonproprietary compounds have plausible rationales for deployment in particular clinical situations but such an "off-label" status means nothing about whether or not a scientific database exists. Lithium carbonate and thyroid hormone are both examples of highly evidence-based adjunctive strategies for treatment-resistant depression, but neither has or likely ever will receive regulatory agency approval for that purpose unless some commercial interest invents a new proprietary formulation or mode of delivery that could justify return on the sizable investment needed for product development. Industry focuses on patented agents for which a lucrative market share is anticipated; clinicians, hopefully, study whether or not a molecule exerts an important pharmacodynamic or pharmacokinetic effect on a definable collection of signs and symptoms.

There is a popular notion in some circles that pharmacotherapy decision-making is largely a trial-and-error process, with little if any guidance from scientifically meaningful parameters to inform treatment choices. Cynics often point to the relative absence of laboratory measures to benchmark treatment success; there is no equivalent of a viral load, white cell count, tumor burden, or ejection fraction to track the impact of a given treatment on the trajectory of a disease process. Yet, clinical yardsticks for measuring success are no different than in other specialties for conditions that lack biomarkers for gauging longitudinal change, as when neurologists judge improvement from chronic headaches (or alleviation of pain in general), or sleep medicine specialists judge efficacy when treating narcolepsy, or otolaryngologists try to ameliorate tinnitus. Even ophthalmologists rely on patient self-report of perceived visual acuity when refracting for corrective lenses. Mental health is no less tangible than other brain functions.

If one insists on iterative psychopharmacology as being a trial-and-error enterprise, we would counter that the notion of "educated guesswork" comes closer to the true nature of informed (rather than random) decision-making. Like the board game Battleship®, in which successive moves against an opponent are made based on knowledge gained from the outcome of previous maneuvers, decisions about "which drug to try next" after an inadequate response to a particular intervention should involve Bayesian analysis – i.e., reflecting the wisdom gained from past efforts and likely reasons for bad outcomes (e.g., drug intolerances, nonadherence, poor symptom targeting, or too narrow a breadth of spectrum, etc.). And, like a good chess player, one is always thinking about the implications of the current move vis-à-vis the next one.

The book is divided into two main sections. The first addresses broad fundamental concepts that inform decision-making in psychopharmacology, including:

- defining evidence-based principles
- how to read and interpret the clinical trials literature, including how to understand study designs, effect sizes, placebo effects, and ways to extrapolate clinical trial findings to routine practice
- understanding dimensions versus categories of psychopathology as the "true" targets of pharmacotherapy, as described in the NIMH Research Domain Criteria (RDoC)
- understanding pharmacodynamic effects as described in the evolving neuroscience-based nomenclature (NbN)
- accounting for drug interactions and cross-tapering strategies
- recognizing when laboratory or other end-organ monitoring is and is not clinically relevant
- recognizing patient-specific moderators and mediators of treatment outcome that can help tailor individualized regimens

- crafting logical and strategic combination drug regimens
- knowing the strengths and limitations of pharmacogenetic testing

When it comes to pharmacotherapy, our sense is that there is all too often a tendency in busy clinical practices to shoot first and ask questions later – that is, an impetus to formulate rapid diagnostic impressions and then let loose with whatever medication strategies seem most expedient to subdue the most offensive symptoms. We favor a more paced and calculated approach when battling psychopathology, one in which the huntsman more stealthily sizes up his quarry, gains familiarity with its habits, behaviors, and relevant characteristics, assures the identified target has indeed been correctly identified, chooses the appropriate weaponry for the task at hand, carefully aligns the crosshairs within his sights before pulling any triggers, and then inflicts as surgically precise an assault with minimal collateral damage as possible. Sir Francis Bacon's adage, "cure the disease and kill the patient" has no place in our concept of sophisticated psychopharmacology. Although our knowledge of disease mechanisms and treatment effects in many ways remains primitive, the maxim *primum non nocere* remains paramount.

It is impossible for any one psychiatrist, no matter how devoted and astute, to grasp the ever-expanding body of relevant research findings. With hundreds if not thousands of clinically relevant peer-reviewed papers appearing in the literature every year, coupled with the challenge of judging quality, relevance, credibility, and distinguishing the compelling from the spurious, the volume of information is crushing. From our perspective, it is more useful to know where to find information and how to apply new knowledge as it emerges, rather than imagining that the corpus of relevant information can be found in a single repository. This book by no means aims to capture every possible morsel of current knowledge (the half-life of which being an iffy proposition in itself), but rather strives to foster for the reader a sense of how to stay up to date and to put basic principles of evidence-based medicine into daily practice. The phrase "I don't know, but I can look it up" is a favorite and empowering statement to tell patients, trainees, and especially ourselves; more than conveying humility, it imparts a disdain for guesswork. Knowing where and how to find and apply accurate information is one of the many no-longer-kept secrets of psychopharmacology that we have tried to share in the pages ahead.

Part II of this book provides specific detail and information on the evidence base and rationales for specific interventions. We seek to focus on the targets of treatment as described in Part I based on their clinical and neuroscientific bases, drawing on dimensions of psychopathology as phenomena that cut across diagnoses (e.g., problems with attention, impulse control, mood, motivation, perception, anxiety, and self-harm). Throughout, our goal is to draw upon the evidence-based clinical trials literature and translate findings into pragmatic takeaways for the busy everyday practitioner. Often this has proven to be harder than we wish it were, especially when the characteristics of our patients only faintly resemble those of research study subjects. Much the way geneticists trying to reconstruct the genome of an extinct species must sometimes "fill in" missing stretches of DNA with data from a next-nearest species, we have tried to use logic and extrapolation to extend our reach in the clinical realm, applying knowledge about the known to the unknown in order to make judicious decisions in managing complex psychiatric presentations.

How best to present all the information in this text in a reader-friendly and clinically pragmatic way? There is no way around detail when discussing the evidence base for a given psychiatric ailment. Our strategy has been to make the process for the reader as engaging and painless as possible through lively text, illustrative cases, figures, plentiful cartoons, lots of "tip" boxes, and interesting facts along the way. Detailed tables that summarize large swaths of information purposely appear at the end of each chapter rather than dispersed within – allowing those who want a deeper dive to do so without breaking the sense of narrative flow for those who may instead prefer more of a gestalt. We are both as deeply committed to how clinicians learn as to *what* they learn. The ability to stay engaged with complex material is no easy task. We hope that our approach successfully stimulates the paralimbic "oh wow!" and "clinical reasoning" circuitry within all learners.

We have both had the good fortune to know and work with many colleagues, mentors, mentees, and patients, who in varied ways provided us with the curiosity, inspiration, and stimulation, to undertake this project. We are especially grateful to many colleagues who have kindly read segments of this book as a work in progress and offered helpful and useful feedback. Lastly, we cannot begin to express proper appreciation to our families, who have so kindly and selflessly been supportive of our professional strivings and inherent drive to educate, advance knowledge, and deliver to our patients the best care possible.

Abbreviations

5HT	serotonin
5HTP	5-hydroxytryptophan
α_7 nAChR	α_7-nicotinic acetylcholine receptor
AA	Alcoholics Anonymous
AAAD	aromatic amino acid decarboxylase
ACC	anterior cingulate cortex
ACE	angiotensin-converting enzyme
ACh	acetylcholine
AChI	acetylcholinesterase inhibitor
ADD	attention deficit disorder
ADHD	attention deficit hyperactivity disorder
AIDS	acquired immune deficiency syndrome
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine transaminase
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANA	antinuclear antibody
ANC	absolute neutrophil count
ANOVA	analysis of variance
ASCVD	atherosclerotic cardiovascular disease
ASD	autism spectrum diorders
ASHP	American Society of Hospital Pharmacists
asp	aspartate
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
BAC	blood alcohol content
BBB	blood–brain barrier
BDD	body dysmorphic disorder
BDNF	brain-derived neurotrophic factor
BEN	benign ethinic neutropenia
BID	twice a day
BMI	body mass index
BMJ	British Medical Journal
bp	base pair
BP	bipolar disorder
BPD	borderline personality disorder
BPDSI	Borderline Personality Disorder Severity Index
BPRS	Brief Psychiatric Rating Scale
BSPS	Brief Social Phobia Scale
CANMAT	Canadian Network for Mood and Anxiety Treatments
CAPS	Clinician-Administered PTSD Scale
CaSR	calcium sensing receptor
CATIE	Clinical Antipsychotics Treatment Intervention Effectiveness
CATIE-AD	Clinical Antipsychotics Treatment Intervention Effectiveness-Alzheimer's Disease
CBC	complete blood count
CBD	cannabidiol
CBI	combined behavioral intervention
CBT	cognitive behavioral therapy
CCK	cholecystokinin
CCPGQ	Criteria for Control of Pathological Gambling Questionnaire
CDP	cytidine-5′-diphosphate
CDT	carbohydrate-deficient transferrin
CGI	Clinical Global Impressions
CGT	complicated grief treatment
CHF	congestive heart failure
CI	confidence interval
CIWA-Ar	Clinical Institute Withdrawal Assessment for Alcohol Revised
CK	creatine kinase
CKD	chronic kidney disease
C-L	consultation-liaison
Cl_{int}	intrinsic clearance
CM	contingency management
CNS	central nervous system
COMT	catechol-*O*-methyltransferase
CONSORT	Consolidated Standards of Reporting Trials

COPD	chronic obstructive pulmonary disease
CoQ	coenzyme Q
COWS	Clinical Opiate Withdrawal Scale
CPIC	Clinical Pharmacogenetics Implementation Consortium
c-PTSD	complex post-traumatic stress disorder
CRD	Centre for Reviews and Dissemination
CRF	corticotropin-releasing factor
CrI	credible interval
CRP	C-reactive protein
CSF	cerebrospinal fluid
CSI	crime scene investigation
CSTC	cortico–striatal–thalamo–cortical
CV	coefficient of variation
cys	cysteine
DA	dopamine
DAAO	*D*-amino acid oxidase
DARE	Database of Abstracts of Reviews of Effects
DAT	dopamine transporter
DBP	diastolic blood pressure
DBT	dialectical behavior therapy
DDI	drug–drug interaction
DHA	docosahexanoic acid
DHEA	dehydroepiandrosterone
DID	dissociative identity disorder
DLPFC	dorsolateral prefrontal cortex
DMPFC	dorsomedial prefrontal cortex
DNA	deoxyribonucleic acid
DOPAC	3,4-dihydroxyphenylacetic acid
DORA	dual orexin receptor antagonist
DRESS	drug reaction with eosinophilia and systemic symptoms
DSHEA	Dietary Supplement Health and Education Act
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IVTR	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision
DST	dexamethasone suppression test
DSST	Digit Symbol Substitution Task
DTs	delerium tremens
DTI	diffusion tensor imaging
DUI	duration of untreated illness
EBM	evidence-based medicine
EC	excitement components
ECNP	European College of Neuropsychopharmacology
ECG	electrocardiogram
ECT	electroconvulsive therapy
EE	expressed emotion
EEG	electroencephalography
eGFR	estimated glomerular filtration rate
EM	extensive metabolizer
EMDR	eye movement desensitization and reprocessing
EPA	eicosopentanoic acid
EPS	extrapyramidal side effects
ER	estrogen receptor
ERP	event-related potential
ES	effect size
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
FA	fractional anisotropy
FDA	US Food and Drug Administration
FDR	false discovery rate
fe	fraction excreted unchanged
FEWP	Free and Easy Wanderer Plus
FGA	first-generation antipsychotic
fMRI	functional magnetic resonance imaging
FOSHU	foods for special health use
FTD	formal thought disorder
FTDR	fixed-tapering-dose regimen
FtM	female to male
FWER	family-wise error rate
GABA	gamma aminobutyric acid
GAD	generalized anxiety disorder
G-CSF	granulocyte colony stimulating factor
GEE	generalized estimating equations

GENDEP	Genome-Based Therapeutic Drugs for Depression Project
GFR	glomerular filtration rate
GGT	gamma-glutamyl transpeptidase
GI	gastrointestinal
GLP-1	glucagon-like peptide 1
glu	glutamate
gly	glycine
GSAS	Gambling Symptom Assessment Scale
GSH	glutathione
GUIDED	Genomics Used To Improve Depression Decisions
GWAS	genome-wide association studies
HAM-A	Hamilton Ratings Scale for Anxiety
HAM-D	Hamilton Ratings Scale for Depression
$HAM-_{D17}$	17-item Hamilton Rating Scale for Depression
HAART	highly active antiretroviral therapy
hGH	human growth hormone
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	hazard ratio
hs-CRP	high-sensitivity C-reactive protein
HVA	homovanillic acid
HWE	Hardy–Weinberg equilibrium
IBS	irritable bowel syndrome
ICD	International Classification of Diseases
ICGDA	International Consensus Group on Depression and Anxiety
ICU	intensive care unit
IED	intermittent explosive disorder
IES	Impact of Events Scale
IL	interleukin
IM	intramuscular
IN	intranasal
IR	immediate release
ISBD-IGSLi	Bipolar Disorders-International Group for the Study of Lithium Treated Patients
iSPOT-D	International Study to Predict Optimised Treatment in Depression
ITT	intent-to-treat
IU	international unit
LAI	long-acting injectable
LD	linkage disequilibrium
LDT	laterodorsal tegmental nuclei
LEE	Level of Expressed Emotion
LHH	likelihood to be helped or harmed
LOCF	last observation carried forward
LSAS	Liebowitz Social Anxiety Scale
LSD	D-lysergic acid diethylamide
MADRS	Montgomery–Åsberg Depression Rating Scale
MAO	monoamine oxidase
MAO-A	monoamine oxidase A
MAO-B	monoamine oxidase B
MAOI	monoamine oxidase inhibitor
MAR	missing at random
MBC	measurement-based care
MCAR	missing completely at random
MCT-1	monocarbylase transport type 1
MCV	mean corpuscular volume
MDD	major depressive disorder
MDD-MF	major depressive disorder with mixed features
MDE	major depressive episode
MDMA	3,4-methylenedioxy-methamphetamine
met	methionine
MFQ	Marks Fear Questionnaire
MGH	Massachusetts General Hospital
mGluR	metabotropic glutamate receptors
MHC	major histocompatibility complex
MI	myocardial infarction
MMRM	mixed models for repeated measures
MMSE	Mini-Mental Status Exam
MOA	mechanism of action
MoCA	Montreal Cognitive Assessment
M/P ratio	maternal milk to plasma ratio
MRI	magnetic resonance imaging
MtF	male to female
MTHFR	methylene tetrahydrofolate reductase
MUPS	medically unexplained symptoms

NAc	nucleus accumbens
NAC	*N*-acetyl-cysteine
NADH	nicotinamide adenine dinucleotide
NaSSA	noradrenergic and specific serotonergic antidepressant
NbN	neuroscience-based nomenclature
NCA	necessary clinical adjustment
NCE	new chemical entity
NDI	nephrogenic diabetes insipidus
NE	norepinephrine
NERI	norepinephrine reuptake inhibitor
NET	norepinephrine transporter
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIMH	National Institute of Mental Health
NMDA	*N*-methyl-D-aspartate
NMS	neuroleptic malignant syndrome
NNH	number needed to harm
NNT	number needed to treat
NO	nitric oxide
NPD	narcissistic personality disorder
NPV	negative predictive value
NSAID	nonsteroidal anti-inflammatory drug
NSDUH	National Survey on Drug Use and Health
NSSI	nonsuicidal self-injury
OCD	obsessive-compulsive disorder
ODD	oppositional-defiant disorder
OFC	orbitofrontal cortex OR olanzapine/fluoxetine combination
OGT	oxygenated glycerol triester
OR	odds ratio
ORA	orexin A
ORB	orexin B
OROS	osmotic-release oral delivery system
pANCA	perinuclear antineutrophil cytoplasmic antibodies
PANSS	Positive and Negative Syndrome Scale
PAPS	3′-phosphoadenosine-5′-phosphosulfate
PAS	Panic and Agoraphobia Scale
PBA	pseudobulbar affect
PCL-C	PTSD Checklist-Civilian Version
PCL-M	PTSD Checklist-Military Version
PCOS	polycystic ovarian syndrome
PCP	phencyclidine
PDE	phosphodiesterase
PDRS	Panic Disorder Rating Scale
PET	positron emission tomography
PFC	prefrontal cortex
PG-CGI	pathological gambling Clinical Global Impressions scale
PG-YBOCS	pathological gambling modification of the Yale–Brown Obsessive-Compulsive Scale
PIM	potentially inappropriate medication
PK	pharmacokinetic
PKC	protein kinase C
PGx	pharmacogenetics
PM	poor metabolizer
PMDD	premenstrual disphoric disorder
PO	by mouth
PPD	postpartum depression
PPHN	persistent pulmonary hypertension in the newborn
PPT	pedunculopontine nuclei
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PRN	as needed
pro	proline
PROSPERO	International Prospective Register of Systematic Reviews
p-SAPK	phosphorylated stress-activated protein kinase
PSM	propensity score matching
PTH	parathyroid hormone
PTSD	post-traumatic stress disorder
qDay	once daily
qEEG	quantitative electroencephalography
qHS	every night at bedtime
QID	four times a day
QTc	corrected QT interval

RBC	red blood cell
RCT	randomized controlled trial
RDC	Research Diagnostic Criteria
RDoC	NIMH Research Domain Criteria
REMS	Risk Evaluation and Mitigation Strategy
RID	relative infant dose
RIMA	reversible inhibitor of MAO-A
RNA	ribonucleic acid
ROC	receiver operating characteristic
RR	relative risk
rTMS	repetitive transcranial magnetic stimulation
SAD	social anxiety disorder
SAH	S-adenosylhomocysteine
SAMe	S-adenosylmethionine
SAMSHA	Substance Abuse and Mental Health Services Administration
SANS	Schedule for the Assessment of Negative Symptoms
SAPK	stress-activated protein kinase
SARI	serotonin antagonist and reuptake inhibitor
SBP	systolic blood pressure
SCIP	Screen for Cognitive Impairment for Psychiatry
ser	serine
SERM	selective estrogen receptor modulator
SERT	serotonin reuptake transporter
SES	socioeconomic status
SGA	second-generation antipsychotic
SHI	Self-Harm Inventory
SIB	self-injurous behavior
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SMD	standard mean difference
SMVT	sodium-dependent multivitamin transporter
SNP	single nucleotide polymorphism
SNRI	serotonin-norepinephrine reuptake inhibitor
SPAI	Social Phobia and Anxiety Inventory
SPECT	single photon emission computed tomography
SPIN	Social Phobia Inventory
SSRI	selective serotonin reuptake inhibitor
STAI	State–Trait Anxiety Inventory
STAXI	State–Trait Anger Expression Inventory
sTNF-R2	soluble tumor necrosis factor receptor 2
STR	symptom-triggered regimen
SUCRA	surface under the cumulative ranking curve
SUD	substance use disorder
SZ	schizophrenia
T_3	triiodothyronine
T_4	thyroxine
TAAR1	trace amine-associated receptor 1
TAU	treatment as usual
TBI	traumatic brain injury
TCA	tricyclic antidepressant
TCI	Temperament and Character Inventory
TD	tardive dyskinesia
TDM	therapeutic drug monitoring
TEAS	treatment-emergent affective switch
TEN	toxic epidermal necrolysis
THC	tetrahydrocannabinol
THF	tetrahydrofolic acid
TID	three times a day
TiME	Time until the need for Intervention for an emerging Mood Episode
TNF	tumor necrosis factor
ToM	theory of mind
TPO	thyroid peroxidase
TPQ	Tridimensional Personality Questionnaire
TRD	treatment-resistant depression
TSH	thyroid-stimulating hormone
UDP	uridine diphosphate
UGT	UDP-glucuronosyl transferase
URM	ultra-rapid metabolizer

VA	US Department of Veterans Affairs
Vd	volume of distribution
VLPFC	ventrolateral prefrontal cortex
VLPO	ventrolateral preoptic nucleus
VMAT2	vesicular monoamine transporter 2
VMPFC	ventromedial prefrontal cortex
VNTR	variable number of tandem repeat
VNS	vagal nerve stimulation
VPC	ventricular premature complexes
VTA	ventral tegmental area
WBC	white blood cell
WCA	World Council of Anxiety
XR	extended release
YBOCS	Yale–Brown Obsessive Compulsive Scale
YMRS	Young Mania Rating Scale
ZAN-BPD	Zanarini Rating Scale for Borderline Personality Disorder