

Stahl's Essential Psychopharmacology

Neuroscientific Basis and Practical Applications

Fifth Edition

Since 1996, students and mental health professionals across the world have turned to Stahl's Essential Psychopharmacology as the single most readable source of information on the fundamentals of psychopharmacology, disease and drug mechanisms. 25 years later, the fifth edition of this bestselling book continues Dr Stahl's proud legacy of helping readers to understand and utilize current therapeutics, and to anticipate the future for novel medications.

Long established as the preeminent source in its field, the eagerly anticipated fifth edition of Dr. Stahl's essential textbook of psychopharmacology is here! With its use of icons and figures that form Dr. Stahl's unique "visual language," the book is the single most readable source of information on disease and drug mechanisms for all students and mental health professionals seeking to understand and utilize current therapeutics, and to anticipate the future for novel medications.

Every aspect of the book has been updated, with the clarity of explanation that only Dr. Stahl can bring. The new edition includes over 500 new or refreshed figures, an intuitive color scheme, 14 new uses for older drugs and 18 brand new drugs, coverage of Parkinson's disease psychosis, behavioral symptoms of dementia, and mixed features in major depressive episodes, and expanded information on the medical uses of cannabis and hallucinogen-assisted psychotherapy.

The opportunity to review and comment on *Stahl's Essential Psychopharmacology*, 5th edition, is truly a pleasure. The depth and comprehension of this edition reads like a fresh view of everything we would want to know in the area of psychopharmacology, including the integration of basic and clinical neuroscience information. The clarity as a teaching tool for any level of education and sophistication is remarkable, just as is the ease of reading and enjoying the unique set of figures and tables. The book represents a departure from the usual fare that we are offered as we delve into the mysteries of our body. In short, this 5th edition is not a simple reworking of earlier editions but really a brand new view. It represents a model for the way that we should cover other areas of neuroscience.

Ellen Frank, PhD, Distinguished Professor
Emeritus of Psychiatry, University of Pittsburgh
School of Medicine

Can you improve on a classic psychopharmacology textbook? Yes! Updated, restyled, and with enhanced illustrations, this 5th edition of Stephen Stahl's "must have" text is comprehensive, readable, and beautifully presented.

Professor David Castle, MD, FRANZCP, FRCPsych,
Scientific Director, Centre for Complex Interventions,
Centre for Addictions and Mental Health, Toronto,
Canada; and Professor, University of Toronto

This new edition of a classical textbook is superb. Unlike most other volumes on psychopharmacology, it is organized around biological mechanisms, and uses that framework to review the latest research. Another unique feature is its use of wonderfully reader-friendly illustrations, bringing to life many pathways that would otherwise be difficult for the non-specialist to understand.

Joel Paris, MD, Emeritus Professor of Psychiatry,
McGill University and Author of "Nature and Nurture in
Mental Disorders: A Gene-Environment Model"

Although the effects of drugs on the mind, via the brain, have preoccupied humans since the dawn of history, the scientific discipline of Psychopharmacology has only developed during modern times. From its inception, Psychopharmacology has always benefitted from a virtuous cycle of science informing clinical practice and clinical questions driving the science. This is now often called "Translational Medicine," an approach that has always been central to Psychopharmacology. Admirable

though this approach is it does present challenges for students, scientists, and clinicians who wish to learn about or keep up with such a diverse, rich, and rapidly evolving knowledge base. *Essential Psychopharmacology* admirably meets these needs for all who wish to learn about or develop their skills and knowledge of psychopharmacology. Written by Dr. Stahl, an author who is a most accomplished clinician, scientist, and teacher, it covers all relevant fields of Psychopharmacology in an expertly informed and accessible way. Previous editions have established *Essential Psychopharmacology* as a vital introductory and reference text for the students and practitioners of psychopharmacology as well as for all scientists with an interest in the field. The latest edition admirably follows its predecessors and will undoubtedly be a vital resource for all those interested in this fascinating discipline.

Professor Allan Young, Chair of Mood Disorders,
Director of the Centre for Affective Disorders,
Department of Psychological Medicine, Institute of
Psychiatry, Psychology and Neuroscience King's College
London

This book is a must for anyone who would like to dive into psychotropics and get a state-of-the-art knowledge in a clear, elegant, and accessible platform.

Professor Stahl has managed to provide simple, yet accurate, cutting-edge concepts using creative and innovative graphics and design. In this regard, it's presenting the perfect marriage of contemporary neuroscience knowledge with outstanding accessibility.

I found this book extremely useful for well-informed clinicians as well as colleagues who are starting to practice psychiatry and recommend it as an essential addition for all mental health professionals as well as for general practitioners with interest in psychiatry.

Professor Joseph Zohar, Director of Psychiatry and
the Anxiety and Obsessive Compulsive Clinic at the Sheba
Medical Center, Tel HaShomer, Israel and Professor of
Psychiatry at Tel Aviv University, Israel

Stahl's Essential Psychopharmacology is without a doubt the leading textbook on the neuroscientific basis of psychopharmacology. It covers the neuroscience relevant to understanding psychotropic drugs and integrates this with the pharmacology of all the main drugs used in practice. This 5th edition is extensively revised and updated to incorporate the latest advances in neuroscience relevant to psychopharmacology. Dr. Stahl has distilled the latest advances in neuroscience

to fully revamp this edition. Dr. Stahl's talent is to make complex ideas deceptively easy to grasp. This is no small feat. He does it with pithy explanations, clear diagrams, and memorable analogies. My favorite is the "Fab Four" of cognition but you'll have to read the book to find out where "The Beatles" come into it. There are many textbooks in the field, but this stands out in the clarity of explanation and cutting-edge neuroscience. True to its name, it is essential reading for psychiatrists, primary care physicians, students, and other professionals treating patients with mental illnesses. It will also be useful for trainees and neuroscientists. In short, Dr. Stahl does it again!

Professor Oliver Howes, MRCPsych, PhD, DM,
 Professor of Molecular Psychiatry, King's College London
 and Imperial College London

Stahl's Essential Psychopharmacology has lived up to its name as "essential" reading for generations of psychiatrists and other professionals involved in the prescription of psychotropic medication at various levels of skill. Its hallmark has always been its approachability while maintaining a depth which still provides important new information for experienced clinicians. The current edition is even more remarkable than its predecessors for its ability to provide useful and indeed essential information at multiple levels of expertise. It is remarkable that something as readable and as approachable at a very basic level can still be incredibly informative to even the most experienced and expert psychopharmacologists. The fully revised diagrams are as ever informative, understandable, and even entertaining. This edition has done what I thought would be impossible in significantly improving on past editions and in producing something that is even more readable and informative to people with a vast range of experience.

Richard J. Porter, Professor of Psychiatry, Head of the Department Psychological Medicine and Director of the Mental Health Clinical Research Unit, University of Otago

Stahl's Essential Psychopharmacology, 5th edition, is truly the preeminent textbook on the pharmacology of psychotropic drugs. It is comprehensive but very readable to both students and practitioners alike.

Dr. Stahl is not only an excellent scientist but also a superb educator, providing a deep understanding of both disease states and drug mechanisms. His unique combination of visual and verbal material makes even the most complex topics approachable. This 5th edition has been extensively revised with hundreds of new or

revised figures, information on 18 new medications, and dozens of other additions or changes. *Stahl's Essential Psychopharmacology* will remain the only pharmacology textbook I recommend to my trainees.

Dr. Richard C. Shelton, Charles Byron Ireland
 Professor, Director, UAB Depression and Suicide Center,
 Department of Psychiatry and Behavior Neurobiology,
 Director of Research, UAB Huntsville Regional Medical
 Campus, School of Medicine, The University of Alabama
 at Birmingham

Stahl's Essential Psychopharmacology is a classic in the field, which is unique in providing not only excellent teaching about mechanisms of drug action through the use of attractive and innovative icons but also a sense of the actual clinical experience of tailoring therapeutic drug choices to psychiatric symptom profiles.

Trevor W. Robbins, Professor of Cognitive
 Neuroscience, University of Cambridge

Steve Stahl's "Essential Psychopharmacology" is a classic, used by clinicians, students, and researchers throughout the world. For clinicians it's practical, for students it's clear, and for researchers it's innovative. Stahl is an experienced clinician, and his text is filled with useful pearls. Stahl is an expert on the principles of medical education; these inform the text and figures, and contribute to their extraordinary impact. Finally, Stahl is a creative researcher, and his framework for thinking about psychiatric medications provides the field with an innovative approach. The 5th edition of the volume is timely, given ongoing work in the field, and has been thoroughly updated to reflect recent advances.

Dan Stein, Professor and Head of the Department of Psychiatry and Mental Health at the University of Cape Town

Stahl's Essential Psychopharmacology, 5th edition, is a masterpiece of impeccable scholarship and the art of education. Signature to Dr. Stahl is this book's tremendous expanse of knowledge that provides not only the science but also clarity in understanding complex concepts of psychiatric psychopharmacology. Dr. Stahl has demonstrated yet again that he is the "people's educator."

Roger S. McIntyre, MD, FRCPC, Professor of Psychiatry and Pharmacology, University of Toronto, Canada Head, Mood Disorders Psychopharmacology Unit and Chairman and Executive Director, Brain and Cognition Discovery Foundation (BCDF), Toronto, Canada

Since its inception, Stahl's Essential Psychopharmacology has been a real treasure for those learning and teaching psychopharmacology and the neuroscience of mental disorders, and as a clinician and medical teacher I have used and warmly recommended each of the four earlier editions. However, this new 5th edition is the best yet in my opinion and resets the bar again for textbooks in this field. It has been extensively revised and brought completely up to date throughout without a major expansion in page count, and covers the entire field comprehensively while retaining the clarity and ease of learning it is famous for. I am pleased to see that with this edition it has moved to a neuroscience-based nomenclature and that many new drugs have been added. A particular strength of this textbook has always been its appeal to visual learners as much as text-based learners through its wealth of figures and captions. These have been impressively updated with a new color scheme and many new figures, so that the book is not only comprehensive and right up to date but is also a real pleasure to read and learn from.

Peter S. Talbot, MD, FRCPsych, Consultant Psychiatrist & Honorary Senior Lecturer, Greater Manchester Mental Health NHS Foundation Trust & University of Manchester

The truth is that this book has a secret: it is obviously a book on pharmacology, but it hides a second one, a book on neuroscience-based psychopathology.

Going back from the receptors to the psychopathological dimensions of the disorders Stahl has his own personal style, starting with his use of the “incipit”: here he makes it clear what he is going to explain to you, and where you have to focus your attention. Concentrate! Then Steve Stahl gives you picture of the determined domain: this time animated in sequences to make you figure concretely the matter of psychopharmacology. At the end, just to make sure that you really grasped the concepts, he repeats everything in a convenient summary, which is very useful to consolidate the knowledge.

Stefano Pallanti, MD, PhD, Professor of Psychiatry and Neurosciences, Director of the Institute for Neurosciences – Florence (IT)

Stahl's Essential Psychopharmacology

Neuroscientific Basis and Practical Applications

Stephen M. Stahl

University of California at Riverside and at San Diego, Riverside and San Diego, California

Editorial Assistant

Meghan M. Grady

With illustrations by

Nancy Muntner

CAMBRIDGE UNIVERSITY PRESS

University Printing House, Cambridge CB2 8BS, United Kingdom

One Liberty Plaza, 20th Floor, New York, NY 10006, USA

477 Williamstown Road, Port Melbourne, VIC 3207, Australia

314–321, 3rd Floor, Plot 3, Splendor Forum, Jasola District Centre,
New Delhi – 110025, India

103 Penang Road #05-06/07, Visioncrest Commercial, Singapore 238467

Cambridge University Press is part of the University of Cambridge.

It furthers the University's mission by disseminating knowledge in the pursuit of education, learning, and research at the highest international levels of excellence.

www.cambridge.org

Information on this title: www.cambridge.org/9781108838573

DOI: 10.1017/9781108975292

First, second, third and fourth edition © Stephen M. Stahl 1996, 2000, 2008, 2013

Fifth edition © Cambridge University Press 2021

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First edition published 1996

Second edition published 2000

Third edition published 2008

Fourth edition published 2013

Fifth edition published 2021

4th printing 2022

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

ISBN 978-1-108-83857-3 Hardback

ISBN 978-1-108-97163-8 Paperback

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Preface to the Fifth Edition

WHAT'S NEW IN THE FIFTH EDITION?

For this fifth edition of *Stahl's Essential Psychopharmacology* you will notice that every figure in the book has been revised, refreshed, and updated with new colors, shading, and outlining. About half the figures are entirely new. The number of chapters has decreased by one, with merger of mood stabilizers into treatments for mood disorders; the text itself and the total number of figures and tables are all approximately the same in length and number, although all chapters have been edited, most of them extensively, with the details of what has changed listed below. The number of references has now been doubled. Overall, 14 drugs have new uses and indications presented, and 18 brand new drugs are introduced and discussed.

Highlights of what has been added or changed since the fourth edition include:

- New coverage of interference RNA (iRNA) in basic neuroscience chapters
- Restructuring all chapters to reflect neuroscience-based nomenclature, that is, drugs named for their mechanism of action rather than use
- Thus, drugs for depression are not “antidepressants” but “monoamine reuptake inhibitors with antidepressant action”; drugs for psychosis are not “antipsychotics” but “serotonin/dopamine antagonists with antipsychotic actions,” etc.
- The psychosis chapter has:
 - new coverage of the direct and indirect striatal dopamine pathways
 - new coverage of trace amines, receptors, and pharmacology
 - revision of the classic dopamine theory of psychosis
 - two new theories of psychosis (serotonin and glutamate)
 - coverage of dementia-related psychosis and Parkinson psychosis in addition to schizophrenia psychosis
 - updated coverage of new indications for drugs previously approved, including lurasidone, cariprazine, and brexpiprazole
- describes five new drugs for psychosis: lumateperone approved, and xanomeline, pimavanserin, trace amine-associated receptor type 1 (TAAR1) agonists, and roluperidone in development
- updated receptor binding data for all drugs
- new coverage of tardive dyskinesia and new drug treatments: deutetrabenazine and valbenazine
- new coverage of uses of serotonin–dopamine drugs for psychosis that are now used even more frequently for depression
- The chapters on mood disorders have:
 - new coverage of mixed mood states
 - new coverage of GABA_A (γ-aminobutyric acid A) receptor subtypes and neurosteroid binding sites
 - new coverage of neurotrophic growth factors and neuroplasticity in depression
 - new coverage of inflammation in depression
 - mood stabilizers redefined
 - new/expanded coverage of levomilnacipran, vortioxetine
 - new coverage of treating cognition in depression
 - new drugs: neuroactive steroids, ketamine/esketamine, dextromethorphan combinations, dextromethadone
 - expanded coverage of treatment resistance and augmentation treatments for monoamine reuptake inhibitors including brexpiprazole, ketamine, esketamine, and trials with cariprazine, pimavanserin
 - expanded coverage of new hypotheses of neuroplastic downstream changes following NMDA (N-methyl-D-aspartate) antagonist therapy with ketamine, esketamine, and others
 - expanded coverage of treating bipolar depression with new indications and new drugs lurasidone, cariprazine
- The anxiety chapter has:
 - removal of obsessive–compulsive disorder (OCD) to the impulsivity chapter
 - coverage of posttraumatic stress disorder (PTSD) as a traumatic disorder rather than anxiety disorder

PREFACE TO THE FIFTH EDITION

- emphasis on anxiety symptoms rather than anxiety disorders
- GABA moved to mood chapter
- revised discussions on treatments of individual anxiety disorders
- renewed emphasis on combining psychotherapy with psychopharmacology for symptoms of anxiety
- The pain chapter has:
 - new criteria for fibromyalgia diagnosis
- The sleep chapter has:
 - much expanded coverage of orexin neuroscience
 - expanded coverage of histamine neuroscience
 - much expanded coverage of neurotransmitters across the sleep/wake cycle
 - presentation of concept of different threshold levels of drugs of different mechanisms in order to induce sleep
 - expanded coverage of dual orexin receptor antagonists including a new agent lemborexant
 - discussion of new H₃ histamine antagonist, pitolisant, for narcolepsy
 - discussion of a new wake-promoting norepinephrine–dopamine reuptake inhibitor (NDRI), solriamfetol
 - expanded circadian rhythm discussion
- The attention deficit hyperactivity disorder (ADHD) chapter has:
 - coverage of multiple new dosage formulations of methylphenidate and amphetamine
 - discussion of new drugs on the horizon: viloxazine, and others
 - a presentation of concept of threshold levels necessary for efficacy of stimulants in ADHD
 - expanded coverage of neurodevelopment in ADHD
- The dementia chapter has:
 - new coverage of acetylcholine and cholinergic receptors
 - introduction of theories for the circuits of memory versus psychosis versus agitation in dementia
 - de-emphasis of the amyloid cascade hypothesis
 - new emphasis on new treatments emerging for the behavioral symptoms of dementia, including pimavanserin for psychosis in all-cause dementia, and brexpiprazole and dextromethorphan/bupropion for agitation in Alzheimer disease
 - expanded coverage of Alzheimer disease and new coverage of vascular dementia, dementia with Lewy bodies, frontotemporal dementia, and Parkinson dementia, clinical characteristics, and neuropathology
- The final chapter on impulsivity, compulsivity, and substance abuse has:
 - new coverage of novel combinations of psychotherapy and hallucinogenic/dissociative drugs for treatment-resistant depression
 - updated and expanded coverage of opioid use disorder and its treatment
 - updated and expanded coverage of the endocannabinoid neurotransmitter system and cannabis use for recreation, abuse, and therapeutics
 - update on Ecstasy and psilocybin
 - update on impulsive–compulsive disorders

WHAT HAS NOT CHANGED IN THE FIFTH EDITION?

What has not changed in this new fifth edition is the didactic style of the first four editions: namely, this text attempts to present the fundamentals of psychopharmacology in simplified and readily readable form. We emphasize current formulations of disease mechanisms and also drug mechanisms. As in previous editions, although the total number of references has been doubled from the fourth edition, the text is not extensively referenced to original papers, but rather to textbooks and reviews and a few selected original papers, with only a limited reading list for each chapter, but preparing the reader to consult more sophisticated textbooks as well as the professional literature.

The organization of information continues to apply the principles of programmed learning for the reader, namely repetition and interaction, which has been shown to enhance retention. Therefore, it is suggested that novices first approach this text by going through it from beginning to end by reviewing only the color graphics and the legends for these graphics. Virtually everything covered in the text is also covered in the graphics and icons. Once having gone through all the color graphics in these chapters, it is recommended that the reader then go back to the beginning of the book, and read the entire text, reviewing the graphics at the same time. After the text has been read, the entire book can be rapidly reviewed again merely by referring to the various color graphics in the book. This mechanism of using the materials will create a certain amount of programmed learning by incorporating the elements of repetition, as well as interaction with visual learning through graphics. Hopefully, the visual concepts learned via graphics will

reinforce abstract concepts learned from the written text, especially for those of you who are primarily “visual learners” (i.e., those who retain information better from visualizing concepts than from reading about them). For those of you who are already familiar with psychopharmacology, this book should provide easy reading from beginning to end. Going back and forth between the text and the graphics should provide interaction. Following review of the complete text, it should be simple to review the entire book by going through the graphics once again.

● HOW HAS THE ESSENTIAL PSYCHOPHARMACOLOGY FAMILY OF BOOKS AND EDUCATIONAL SERVICES GROWN?

Expansion of *Essential Psychopharmacology* Books

The fifth edition of *Essential Psychopharmacology* is the flagship of this book series, but not the entire fleet, as the *Essential Psychopharmacology* Series has further expanded. For those of you interested, there is an entire suite of dozens of books and extensive online information now available that accompany *Essential Psychopharmacology*, Fifth Edition. There are now six prescriber's guides:

- for psychotropic drugs, *Stahl's Essential Psychopharmacology: the Prescriber's Guide*, now in its seventh edition
- for psychotropic drugs specifically for use in children and adolescents, *Stahl's Essential Psychopharmacology Prescribers Guide: Children and Adolescents*
- for neurology drugs, *Essential Neuropharmacology: the Prescriber's Guide*, second edition.
- for pain drugs: *Essential Pain Pharmacology: the Prescriber's Guide*
- for drugs to treat serious mental illnesses particularly in forensic settings, a new book, *Management of Complex Treatment Resistant Psychotic Disorders* (with Michael Cummings)
- for the UK, there will soon be published a *Cambridge Prescribers Guide* for psychotropic drugs to fit into UK practice patterns (with Sep Hafizi and Peter Jones)

For those interested in how the textbook and prescriber's guides get applied in clinical practice there are now three books of case studies:

- *Case Studies: Stahl's Essential Psychopharmacology*, covering 40 cases from my own clinical practice

- *Case Studies*, 2nd edition, with cases from Tom Schwartz's practice at State University of New York Syracuse
- *Case Studies*, 3rd edition, with cases from the University of California Riverside Department of Psychiatry (with Takesha Cooper and Gerald Maguire)

For those teachers and students wanting to assess objectively their expertise, to pursue maintenance of certification credits for board recertification in psychiatry in the US, and for background on instructional design and how to teach, there are two books:

- *Stahl's Self Assessment Examination in Psychiatry: Multiple Choice Questions for Clinicians*, now in its third edition
- *Best Practices in Medical Teaching*

For those interested in expanded visual coverage of specialty topics in psychopharmacology, there is the *Stahl's Illustrated* series:

- *Antidepressants*
- *Antipsychotics: Treating Psychosis, Mania and Depression*, 2nd edition
- *Mood Stabilizers*
- *Anxiety, Stress, and PTSD*
- *Attention Deficit Hyperactivity Disorder*
- *Chronic Pain and Fibromyalgia*
- *Substance Abuse and Impulsive Disorders*
- *Violence: Neural Circuits, Genetics, and Treatment*
- *Sleep and Sleep Wake Disorders*
- *Dementia*

For practical and in-depth management tips and guidance, a newly introduced *Handbook* series:

- *The Clozapine Handbook* (with Jonathan Meyer)
- *Handbook of Psychotropic Drug Levels* (with Jonathan Meyer)
- *Suicide Prevention Handbook* (with Christine Moutier and Anthony Pisani)

Finally, there is an ever-growing edited series of subspecialty topics:

- *Practical Psychopharmacology* (applying evidence-based studies to treatment, with Joe Goldberg)
- *Violence in Psychiatry* (with Katherine Warburton)
- *Decriminalizing Mental Illness* (with Katherine Warburton)
- *Evil, Terrorism and Psychiatry* (with Donatella Marazitti)
- *Next Generation Antidepressants*

PREFACE TO THE FIFTH EDITION

- *Essential Evidence-Based Psychopharmacology*, 2nd edition
- *Essential CNS Drug Development*
- *Cambridge Textbook of Neuroscience for Psychiatrists* (with Mary-Ellen Lynall and Peter Jones)

Online Options***Essential Psychopharmacology Online***

Now, you also have the option of accessing all these books plus additional features online by going to *Essential Psychopharmacology Online* at www.stahlonline.org.

In addition, www.stahlonline.org is now linked to:

- the journal *CNS Spectrums*, www.journals.Cambridge.org/CNS,

of which I am the editor-in-chief, and which is the official journal of the Neuroscience Education Institute (NEI), free online to NEI members. This journal features readable and illustrated reviews of current topics in psychiatry, mental health, neurology, and the neurosciences as well as psychopharmacology

The NEI Website, www.neiglobal.com

- Access CME credits for this and other books in the Stahl series
- Access the Master Psychopharmacology Program, an assessment-based certificate program that covers all of the content in *Stahl's Essential Psychopharmacology*
- Purchase downloadable PowerPoint slides of all the figures in this book

Hopefully the reader can appreciate that this is an incredibly exciting time for the fields of neuroscience and mental health, creating fascinating opportunities for clinicians to utilize current therapeutics and to anticipate future medications that are likely to transform the field of psychopharmacology. Best wishes for your first step on this fascinating journey.

Stephen M. Stahl, MD, PhD, DSc (Hon.)
*In memory of Daniel X. Freedman, mentor,
colleague, and scientific father
To Shakila*

CME Information

Release/expiration dates

Released: May 1, 2021

CME credit expires: May 1, 2024

Learning objectives

After completing this activity, you should be better able to:

- Describe the neuropathology underlying mental health disorders
- Describe the differential neurobiological targets for psychotropic medications
- Link the mechanisms of psychotropic medications to their clinical targets

Accreditation and credit designation statements

The Neuroscience Education Institute (NEI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

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The content was peer-reviewed by an MD, PsyD, or PhD specializing in psychiatry to ensure the scientific accuracy and medical relevance of information presented and its independence from bias. NEI takes responsibility for the content, quality, and scientific integrity of this CME activity.

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Author

Stephen M. Stahl, MD, PhD, DSc (Hon.)

Clinical Professor, Department of Psychiatry and Neuroscience, University of California, Riverside School of Medicine, Riverside, CA

Adjunct Professor, Department of Psychiatry, University of California, San Diego School of Medicine, La Jolla, CA
Honorary Visiting Senior Fellow, University of Cambridge, Cambridge, UK

Director of Psychopharmacology Services, California Department of State Hospitals, Sacramento, CA

Grant/Research: Acadia, Avanir, Braeburn, Intra-Cellular, Ironshore, Lilly, Neurocrine, Otsuka, Sunovion

Consultant/Advisor: Acadia, Alkermes, Allergan, Arbor, Axovant, Axsome, Celgene, ClearView, Concert, EMD Serono, Eisai, Ferring, Impel, Intra-Cellular, Ironshore, Janssen, Lilly, Lundbeck, Merck, Otsuka, Pfizer, Sage, Servier, Sunovion, Takeda, Taliaz, Teva, Tonix, Tris, Vifor

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Content Editor**Meghan M. Grady, BA**

*Vice President, Content Development, Neuroscience
Education Institute, Carlsbad, CA*

No financial relationships to disclose.

Editorial Staff**Gabriela Alarcón, PhD**

*Medical Writer, Neuroscience Education Institute,
Carlsbad, CA*

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her spouse/partner.

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Communications

Peer Reviewers**William M. Sauvé, MD**

*Regional Medical Director, Greenbrook TMS NeuroHealth
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Speakers Bureau: Avanir

Donna M. Wilcock, PhD

*Assistant Dean of Biomedicine; Associate Director, Outreach
and Partnerships; Sanders-Brown Center on Aging; Sweeney-
Nelms Professor in Alzheimer's Disease Research, Alzheimer's
Disease Center; Associate Professor, Department of Physiology;
University of Kentucky College of Medicine, Lexington, KY*

Consultant/Advisor: AC Immune, Alector, AvroBio

The Planning Committee, Editorial, and Design

Staff, and remaining **Peer Reviewers** have no financial
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