

# Stahl's Essential Psychopharmacology

## Neuroscientific Basis and Practical Application

### Fourth Edition

With this fully revised Fourth Edition, Dr. Stahl returns to the essential roots of what it means to become a neurobiologically empowered psychopharmacologist, expertly guided in the selection and combination of treatments for individual patients in practice.

Embracing the unifying themes of “symptom endophenotypes,” dimensions of psychopathology that cut across syndromes, and “symptoms and circuits,” every aspect of the text has been updated to the frontiers of current knowledge, with the clarity of explanation and illustration that only Dr. Stahl can bring.

Integrating much of the basic neuroscience into the clinical chapters, and with major additions in the areas of psychosis, antipsychotics, antidepressants, impulsivity, compulsivity, and addiction, this is the single most readily readable source of information on disease and drug mechanisms.

This remains the essential text for all students and professionals in mental health seeking to understand and utilize current therapeutics, and to anticipate the future for novel medications.

# Stahl's Essential Psychopharmacology

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Neuroscientific Basis and Practical Application

**Fourth Edition**

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with illustrations by

**Nancy Muntner**



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In memory of Daniel X. Freedman, mentor, colleague, and scientific father  
To Cindy, Jennifer, and Victoria

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## Preface to the fourth edition

For this fourth edition of *Stahl's Essential Psychopharmacology* you will notice there is a new look and feel. With a new layout, displayed over two columns, and an increased page size we have eliminated redundancies across chapters, have added significant new material, and yet have decreased the overall size of the book.

**Highlights** of what has been added or changed since the 3rd edition include:

- Integrating much of the basic neurosciences into the clinical chapters, thus reducing the number of introductory chapters solely covering basic neurosciences.
- Major revision of the psychosis chapter, including much more detailed coverage of the neurocircuitry of schizophrenia, the role of glutamate, genomics, and neuroimaging.
- One of the most extensively revised chapters is on antipsychotics, which now has:
  - new discussion and illustrations on how the current atypical antipsychotics act upon serotonin, dopamine, and glutamate circuitry
  - new discussion of the roles of neurotransmitter receptors in the mechanisms of actions of some but not all atypical antipsychotics
    - 5HT<sub>7</sub> receptors
    - 5HT<sub>2C</sub> receptors
    - α<sub>1</sub>-adrenergic receptors
  - completely revamped visuals for displaying the relative binding properties of 17 individual antipsychotics agents, based upon log binding data made qualitative and visual with novel graphics
  - reorganization of the known atypical antipsychotics as
    - the “pines” (peens)
    - the “dones”
      - two “pips”
      - and a “rip”
- inclusion of several new antipsychotics
  - iloperidone (Fanapt)
  - asenapine (Saphris)
  - lurasidone (Latuda)
- extensive coverage of switching from one antipsychotic to another
- new ideas about using high dosing and polypharmacy for treatment resistance and violence
- new antipsychotics in the pipeline
  - brexpiprazole
  - cariprazine
  - selective glycine reuptake inhibitors (SGRIs, e.g., bitopertin [RG1678], Org25935, SSR103800)
- The mood chapter has expanded coverage of stress, neurocircuitry, and genetics.
- The antidepressant and mood stabilizer chapters have:
  - new discussion and illustrations on circadian rhythms
  - discussion of the roles of neurotransmitter receptors in the mechanisms of actions of some antidepressants
    - melatonin receptors
    - 5HT<sub>1A</sub> receptors
    - 5HT<sub>2C</sub> receptors
    - 5HT<sub>3</sub> receptors
    - 5HT<sub>7</sub> receptors
    - NMDA glutamate receptors
- inclusion of several new antidepressants
  - agomelatine (Valdoxan)
  - vilazodone (Viibryd)

## Preface

- vortioxetine (LuAA21004)
- ketamine (rapid onset for treatment resistance)
- The anxiety chapter provides new coverage of the concepts of fear conditioning, fear extinction, and reconsolidation, with OCD moved to the impulsivity chapter.
- The pain chapter updates neuropathic pain states.
- The sleep/wake chapter provides expanded coverage of melatonin and new discussion of orexin pathways and orexin receptors, as well as new drugs targeting orexin receptors as antagonists, such as:
  - suvorexant/MK-6096
  - almorexant
  - SB-649868
- The ADHD chapter includes new discussion on how norepinephrine and dopamine tune pyramidal neurons in prefrontal cortex, and expanded discussion on new treatments such as:
  - guanfacine ER (Intuniv)
  - lisdexamfetamine (Vyvanse)
- The dementia chapter has been extensively revamped to emphasize the new diagnostic criteria for Alzheimer's disease, and the integration of biomarkers into diagnostic schemes including:
  - Alzheimer's diagnostics
    - CSF A $\beta$  and tau levels
    - amyloid PET scans, FDG-PET scans, structural MRI scans
  - multiple new drugs in the pipeline targeting amyloid plaques, tangles, and tau
    - vaccines/immunotherapy (e.g., bapineuzumab, solenezumab, crenezumab), intravenous immunoglobulin
    - $\gamma$ -secretase inhibitors (GSIs, e.g., semagacestat)
    - $\beta$ -secretase inhibitors (e.g., LY2886721, SCH 1381252, CTS21666, others)
- The impulsivity–compulsivity and addiction chapter is another of the most extensively revised chapters in this fourth edition, significantly expanding the drug abuse chapter of the third edition to include now a large number of related “impulsive–compulsive” disorders that hypothetically share the same brain circuitry:
  - neurocircuitry of impulsivity and reward involving the ventral striatum
  - neurocircuitry of compulsivity and habits including drug addiction and behavioral addiction involving the dorsal striatum
  - “bottom-up” striatal drives and “top-down” inhibitory controls from the prefrontal cortex
  - update on the neurobiology and available treatments for the drug addictions (stimulants, nicotine, alcohol, opioids, hallucinogens, and others)
  - behavioral addictions
    - major new section on obesity, eating disorders, and food addiction, including the role of hypothalamic circuits and new treatments for obesity
    - lorcaserin (Belviq)
    - phentermine/topiramate ER (Qsymia)
    - bupropion/naltrexone (Contrave)
    - zonisamide/naltrexone
    - obsessive–compulsive and spectrum disorders
    - gambling, impulsive violence, mania, ADHD and many others

One of the major themes emphasized in this new edition is the notion of **symptom endophenotypes**, or dimensions of psychopathology that cut across numerous syndromes. This is seen perhaps most dramatically in the organization of numerous disorders of impulsivity/compulsivity, where impulsivity and/or compulsivity are present in many psychiatric conditions and thus “travel” trans-diagnostically without respecting the DSM (*Diagnostic and Statistical Manual*) of the American Psychiatric Association or the ICD (*International Classification of Diseases*). This is the future of psychiatry – the matching of symptom endophenotypes to hypothetically malfunctioning brain circuits, regulated by genes, the environment, and neurotransmitters. Hypothetically, inefficiency of information processing in these brain circuits creates symptom expression in various psychiatric disorders that can be changed with psychopharmacologic agents. Even the DSM recognizes this concept and calls it Research Domain Criteria (or RDoC). Thus, impulsivity and compulsivity can be seen as domains of psychopathology; other domains include mood, cognition, anxiety, motivation, and many more. Each chapter in this fourth edition discusses “symptoms

and circuits” and how to exploit domains of psychopathology both to become a neurobiologically empowered psychopharmacologist, and to select and combine treatments for individual patients in psychopharmacology practice.

What has not changed in this new edition is the **didactic style** of the first three editions. 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, 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, reviewing only the color graphics and the legends for those 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.

## Expansion of *Essential Psychopharmacology* books

This fourth edition of *Essential Psychopharmacology* is the flagship, but not the entire fleet, as the *Essential Psychopharmacology* series has expanded now to an entire suite of products for the interested reader. For those of you interested in specific prescribing information, there are now three prescriber's guides:

- for psychotropic drugs, *Stahl's Essential Psychopharmacology: the Prescriber's Guide*
- for neurology drugs, *Essential Neuropharmacology: the Prescriber's Guide*
- for pain drugs: *Essential Pain Pharmacology: the Prescriber's Guide*

For those interested in how the textbook and prescriber's guides get applied in clinical practice there is a book covering 40 cases from my own clinical practice:

- *Case Studies: Stahl's Essential Psychopharmacology*

For teachers and students wanting to assess objectively their state of 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*
- *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
- *Anxiety, Stress, and PTSD*
- *Attention Deficit Hyperactivity Disorder*
- *Chronic Pain and Fibromyalgia*
- *Mood Stabilizers*
- *Substance Use and Impulsive Disorders*

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

- *Next Generation Antidepressants*
- *Essential Evidence-Based Psychopharmacology*, 2nd edition
- *Essential CNS Drug Development*



## Preface

### *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](http://www.stahlonline.org). We are proud to announce the continuing update of this new website which allows you to search online within the entire *Essential Psychopharmacology* suite of products. With publication of the fourth edition, two new features will become available on the website:

- downloadable slides of all the figures in the book
- narrated animations of several figures in the textbook, hyperlinked to the online version of the book, playable with a click

In addition, [www.stahlonline.org](http://www.stahlonline.org) is now linked to:

- our new journal *CNS Spectrums* ([www.journals.cambridge.org/CNS](http://www.journals.cambridge.org/CNS)), of which I am the new editor-in-chief, and which is now the official journal of the Neuroscience Education Institute (NEI), free online to NEI members. This journal now 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](http://www.neiglobal.com):
  - for CME credits for reading the books and the journal, and for completing numerous additional programs both online and live
  - for access to the live course and playback encore features from the annual NEI Psychopharmacology Congress
  - for access to the NEI Master Psychopharmacology Program, an online fellowship with certification
- plans for expansion to a Cambridge University Health Partners co-accredited online Masterclass and Certificate in Psychopharmacology, based upon live programs held on campus in Cambridge and taught by University of Cambridge faculty, including myself, having joined the faculty there as an Honorary Visiting Senior Fellow

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*

## CME Information

### Release/expiration dates

Originally released: February 1, 2013  
 Reviewed and re-released: February 1, 2016  
 CME credit expires: January 31, 2019

### Target audience

This activity has been developed for prescribers specializing in psychiatry. All other health care providers interested in psychopharmacology are welcome for advanced study, especially primary care physicians, nurse practitioners, psychologists, and pharmacists.

### Statement of need

Psychiatric illnesses have a neurobiological basis and are primarily treated by pharmacological agents; understanding each of these, as well as the relationship between them, is essential in order to select appropriate treatment for a patient. The field of psychopharmacology has experienced incredible growth; it has also experienced a major paradigm shift from a limited focus on neurotransmitters and receptors to an emphasis as well upon brain circuits, neuroimaging, genetics, and signal transduction cascades.

The following unmet needs and professional practice gaps regarding mental health were revealed following a critical analysis of activity feedback, expert faculty assessment, literature review, and through new medical knowledge:

- Mental disorders are highly prevalent and carry substantial burden that can be alleviated through treatment; unfortunately, many patients with mental disorders do not receive treatment or receive suboptimal treatment.
- There is a documented gap between evidence-based practice guidelines and actual care in clinical practice for patients with mental illnesses. This gap is due at least in part to lack of clinician

confidence and knowledge in terms of appropriate usage of the therapeutic tools available to them.

To help address clinician performance gaps with respect to diagnosis and treatment of mental health disorders, quality improvement efforts need to provide education regarding (1) the fundamentals of neurobiology as it relates to the most recent research regarding the neurobiology of mental illnesses; (2) the mechanisms of action of treatment options for mental illnesses and the relationship to the pathophysiology of the disease states; and (3) new therapeutic tools and research that are likely to affect clinical practice.

### Learning objectives

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

- Apply fundamental principles of neurobiology to the assessment of psychiatric disease states
- Differentiate the neurobiological targets for psychotropic medications
- Link the relationship of psychotropic drug mechanism of action to the pathophysiology of disease states
- Identify novel research and treatment approaches that are expected to affect clinical practice

### Accreditation and credit designation statements

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

The Neuroscience Education Institute designates this enduring material for a maximum of 67.0 *AMA PRA Category 1 Credits*<sup>™</sup>. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

### CME information

**Nurses:** for all of your CNE requirements for recertification, the ANCC will accept *AMA PRA Category 1 Credits™* from organizations accredited by the ACCME. The content of this activity pertains to pharmacology and is worth 67.0 continuing education hours of pharmacotherapeutics.

**Physician Assistants:** the NCCPA accepts *AMA PRA Category 1 Credits™* from organizations accredited by the AMA (providers accredited by the ACCME).

A certificate of participation for completing this activity will also be available.

#### Optional posttests and CME credit instructions

The estimated time for completion of this activity is 67 hours. Optional certificates of CME credit or participation are available for each topical section of the book (total of twelve sections). There is a fee for each posttest (varies per section) which is waived for NEI members.

1. Read the desired topical section, evaluating the content presented
2. Complete the related posttest, available only online at [www.neiglobal.com/CME](http://www.neiglobal.com/CME) (under "Book")
3. Print your certificate (if a score of 70% or more is achieved)

Questions? Call 888-535-5600, or email [CustomerService@NEIglobal.com](mailto:CustomerService@NEIglobal.com)

#### Peer review

The content was originally peer-reviewed in 2013 by 3 MDs and a PharmD to ensure the scientific accuracy and medical relevance of information presented and its independence from commercial bias. The content was reviewed again in 2016 to verify it is still up-to-date and accurate. The Neuroscience Education Institute takes responsibility for the content, quality, and scientific integrity of this CME activity.

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A variety of resources addressing cultural and linguistic competency can be found at this link: [nei.global/CMEregs](http://nei.global/CMEregs)

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